The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Epilim and Depakote SmPCs and PILs

Published April 2020

Contents

Epilim – datasheets and summary of product characteristics

1975

Reckitt-Labaz
Reckitt & Colman
Pharmaceutical Division
Hull HU8 7DS

EPILIM*

Presentation Epilim is available as a scored white tablet with a diameter of 11 mm. The active ingredient is sodium valproate (200 mg per tablet).

Uses For use in generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment.

Dosage and administration Adults and children over 15 years: Epilim can be introduced alone or added to existing treatment.

New patients: Treatment should start with 1 tablet three times daily. Dosage may be increased after three days to 2 tablets three times daily. If, after a total period of two weeks, adequate control has not been achieved, dosage of Epilim should again be increased and one other anti-epileptic agent may be introduced commencing at a low dosage. Dosage of both Epilim and other agents should then be adjusted during the stabilisation period to obtain optimum control.

Patients receiving other therapy: Treatment should start with 1 tablet twice a day. Dosage can be increased at intervals of three days in increments of 2 tablets per day; optimum control is achieved usually within the dosage range of 4–7 tablets (800–1,400 mg) per day. (However, in several recently published controlled trials, it was found that the dose could be increased with advantage to 2.4 g per day, to achieve control in very severe cases.)

Dosage of existing medication may be reduced concomitantly to obtain optimum control on a minimum dosage combination of drugs. It may be possible to withdraw the concomitant therapy, allowing optimum control with Epilim alone (e.g. in petit mal with absence). If increased sedation is observed, dosage of barbiturates should be concomitantly reduced as the dosage of Epilim is increased.

Tablets should be swallowed whole, with a little water if necessary (but *not* with aerated mineral water).

Children under 15 years and infants: Dosage should be related to age within the range as follows:

0–3 years: Usually 20–30 mg/kg/day.

3–15 years: Dosage should range from 2 tablets to doses slightly less than those of adults.

All doses should be tailored to obtain optimum control and the treatment procedure should follow the same principle as in adults.

Contra-indications, warnings, etc *Contra-indications:* There are no specific contra-indications for Epilim, but note should be taken of the following precautions.

Precautions — General: No hepatic, renal, cardiac or haematological effects attributable to Epilim have been reported. At the start of treatment a few patients have experienced minor gastric irritation and, less frequently, nausea. Should these symptoms persist, they can be relieved by standard medication.

Combined medication: Epilim is well tolerated in combination with other anti-epileptic agents. Epilim may enhance the sedative effects of other agents, particularly barbiturates; this should be recognised when introducing Epilim to existing treatment, and may require concomitant reduction in the dosage of other agents. Similarly Epilim, in common with many other medications, may potentiate the effect of monoamine oxidase inhibitors (MAOI) and thymoleptics, and the doses of these agents should be reduced accordingly.

Diabetic patients: Epilim is partially eliminated by the renal route in the form of ketone bodies, and this may give false positives when testing the urine of possible diabetics.

Overdosage: Reports of accidental overdosage of Epilim have been rare. Recovery after the ingestion of up to 30 g has been uneventful following conservative management.

As Epilim is absorbed very rapidly, gastric lavage may be of limited value. However, as Epilim is excreted almost entirely within 24 hours (70% in the urine), it is recommended that general supportive measures be applied, paying particular attention to the maintenance of an adequate urinary output.

Precautions — women of child bearing age: This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.

Pharmaceutical precautions The tablets, being hygroscopic, must be kept in their protective foil until taken, and should be stored in a cool dry place.

Legal category Available on prescription only.

Package quantities Carton containing 100 tablets in foil.

Further information Epilim represents a new approach in the therapy of epilepsy. Whereas most of the currently available drugs have chemical features in common, Epilim is a different entity with a simple chemical structure which (unlike existing drugs) does not contain nitrogen. Biological studies on Epilim indicate that it may have a different mode of action in that it produces an increase in the level of γ-aminobutyric acid (GABA) in the brain by inhibiting GABA transaminase, which is responsible for the breakdown of GABA. Although there is no simple correlation between convulsive activity and GABA levels, evidence linking them is growing.

Clinically Epilim is effective in treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

Product licence number 0623/0001.

**Trade Mark*

1976

Reckitt-Laboz
Reckitt & Colman Pharmaceutical Division
Dansom Lane
Hull HU8 7DS

EPILIM® ▽

Presentation Epilim is available as a scored white tablet with a diameter of 11 mm. The active ingredient is sodium valproate (200 mg per tablet).

Uses For use in generalised, focal or other epilepsy. In women of child-bearing age, the product should be used only in severe cases or in those resistant to other treatment.

Dosage and administration *Adults and children over 15 years:* Epilim can be introduced alone or added to existing treatment.

New patients: Treatment should start with 1 tablet three times daily. Dosage may be increased after three days to 2 tablets three times daily. If, after a total period of two weeks, adequate control has not been achieved, dosage of Epilim should again be increased and one other anti-epileptic agent may be introduced, commencing at a low dosage. Dosage of both Epilim and other agents should then be adjusted during the stabilisation period to obtain optimum control.

Patients receiving other therapy: Treatment should start with 1 tablet three times a day. Dosage can be increased at intervals of three days in increments of 2 tablets per day; optimum control is achieved usually within the dosage range of 4–7 tablets (800–1,400 mg) per day. (However, in several recently published controlled trials, it was found that the dose could be increased with advantage to 2.4 g per day, to achieve control in very severe cases.)

Dosage of existing medication may be reduced concomitantly to obtain optimum control on a minimum dosage combination of drugs. It may be possible to withdraw the concomitant therapy, allowing optimum control with Epilim alone (e.g. in petit mal with absence). If increased sedation is observed, dosage of barbiturates should be concomitantly reduced as the dosage of Epilim is increased.

Tablets should be swallowed whole, with a little water and with or after food. Aerated mineral water, or other aerated drinks, should not be used.

Children under 15 years and infants: Dosage should be related to age within the range as follows.

0–3 years: Usually 20–30 mg/kg/day.

3–15 years: Dosage should range from 2 tablets to doses slightly less than those of adults.

All doses should be tailored to obtain optimum control and the treatment procedure should follow the same principle as in adults.

Contra-indications, warnings, etc *Contra-indications:* There are no specific contra-indications for Epilim, but note should be taken of the following precautions.

Precautions – General: No hepatic, renal, cardiac or haematological effects attributable to Epilim have been reported. At the start of treatment a few patients have experienced minor gastric irritation and, less frequently, nausea. Should these symptoms persist, they can be relieved by standard medication.

Combined medication: Epilim is well tolerated in combination with other anti-epileptic agents. Epilim may enhance the sedative effects of other agents, particularly barbiturates; this should be recognised when introducing Epilim to existing treatment, and may require concomitant reduction in the dosage of other agents. Similarly Epilim, in common with many other medications, may potentiate the effect of monoamine oxidase inhibitors (MAOI) and other anti-depressants, and the doses of these agents should be reduced accordingly.

Diabetic patients: Epilim is partially eliminated by the renal route in the form of ketone bodies, and this may give false positives when testing the urine of possible diabetics.

Overdosage: Reports of accidental overdosage of Epilim have been rare. Recovery after the ingestion of up to 30 g has been uneventful following conservative management.

As Epilim is absorbed very rapidly, gastric lavage may be of limited value. However, as Epilim is excreted almost entirely within 24 hours (70% in the urine), it is recommended that general supportive measures be applied, paying particular attention to the maintenance of an adequate urinary output.

Precautions – women of child bearing age: This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.

Pharmaceutical precautions The tablets, being hygroscopic, must be kept in their protective foil until taken, and should be stored in a cool dry place.

Legal category S62.

Package quantities Carton containing 100 tablets in foil.

Further information Epilim represents a new approach in the therapy of epilepsy. Whereas most of the currently available drugs have chemical features in common, Epilim is a different entity with a simple chemical structure which (unlike existing drugs) does not contain nitrogen. Biological studies on Epilim indicate that it may have a different mode of action in that it produces an increase in the level of γ-aminobutyric acid (GABA) in the brain. Although there is no simple correlation between convulsive activity and GABA levels, evidence linking them is growing.

Clinically Epilim is effective in treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

Product licence number 0623/0001.

**Trade Mark*

1977

Reckitt-Labaz
Reckitt & Colman Pharmaceutical Division
Dansom Lane
Hull HU8 7DS

EPILIM® ▽

Presentation Epilim is available as a scored, white tablet (11 mm diameter) and as a red, cherry-flavoured syrup. The active ingredient is sodium valproate (200 mg per tablet or per 5 ml syrup).

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; the tablets should be swallowed whole, if necessary with a little water, but not aerated water.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,500 mg/day, or one other anti-epileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; dosage of both Epilim and other agents should be adjusted during the stabilisation period, to give optimum control at the lowest possible combined-dosage level, and it may be found possible to maintain control with Epilim alone.

Children over 20 kg: Initial dosage should be 400 mg/day irrespective of weight, in divided doses, with spaced increases until control is achieved. This is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, up to 50 mg/kg/day.

A dose of 50 mg/kg should be exceeded only in patients in whom plasma levels are measured; plasma levels of 200 µg/ml should be exceeded only with caution, and with monitoring of haematological function.

Once known enzyme-inducers, such as phenobarbitone or primidone, have been withdrawn, or if side effects, such as tremor, are experienced, it may be possible to reduce the dose of Epilim while still maintaining seizure control. A method of measuring plasma levels is available, should this be considered helpful; however, seizure control must ultimately determine the optimum dosage.

Contra-indications, warnings, etc There are no absolute contra-indications, but the following precautions should be noted:

Adverse reactions: No hepatic, renal or cardiac effects attributable to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome if Epilim is taken with or after food; should such symptoms persist, they can be relieved by standard medication. Transient hair loss has been noted in a few patients. Tremor has been seen occasionally, at high dosages. Prolongation of bleeding-time, sometimes with thrombocytopenia, has occurred, rarely, at high dosages. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigation. It is recommended that patients receiving Epilim should be monitored for platelet function before major surgery.

Combined medication: Epilim is well tolerated in combination with other antiepileptic agents, but may enhance their sedative effects, particularly those of barbiturates; thus, when Epilim is added to existing treatment, dosage of other drugs may need to be reduced. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors (MAOI) and other antidepressants, and dosages of such agents should be reduced accordingly.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partially in the form of ketone bodies, and this may give false positives in the urine-testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Overdosage: Few cases of accidental overdosage have been reported, and recovery after ingestion of up to 30 g has been uneventful, with conservative management.

Epilim is absorbed very rapidly, so gastric lavage may be of limited value. However, as Epilim is excreted almost entirely within 24 hours (70% in the urine), general supportive measures are recommended, with special attention to the maintenance of an adequate urinary output.

Women of child-bearing age: Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of child-bearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Pharmaceutical precautions As Epilim tablets are hygroscopic, they must be kept in their protective foil until taken; they should be stored in a cool dry place. Epilim Syrup should be kept in a cool place away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup the recommended diluent is Syrup BP. The diluted product will have a 14 day shelf life.

Legal category S52.

Package quantities Cartons of 100 tablets in foil, and bottles of 200 ml syrup.

Further information Epilim represents a new approach in the therapy of epilepsy. Its simple chemical structure, containing no nitrogen, differs widely from that of other currently available anticonvulsant drugs, and biological studies suggest that it may have a different mode of action, producing an increase in the level of gamma-aminobutyric acid (GABA) in the brain. Although there is no simple correlation between GABA and convulsive activity, evidence linking them is growing. Epilim is clinically effective in the treatment of petit

mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

References: Barnes, S. E. & Bower, B. D. (1975). *Develop. Med. Child Neurol.* **17**, *175–81*
Jeavons, P. M. & Clark, J. E. (1974): *Brit. med. J.* **2**, *564–6.*
Richens, A. & Ahmad, S. (1975): *Brit. med. J.* **4**, *255–6.*
Haigh, D. & Forsythe, W. I. (1975): *Develop. Med. Child Neurol.* **17**, *743–6.*
Clinical and Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy. *Proceedings of a Symposium held at Nottingham University* 23–4 September 1976. MCS Consultants, England, 1976

Product licence numbers
Tablets 0523/0001
Syrup 0523/0004

*Trade Mark

1978

Reckitt-Labaz
Reckitt & Colman Pharmaceutical Division
Dansom Lane
Hull HU8 7DS

EPILIM®

Presentation 1. A white scored tablet containing 200 mg sodium valproate.
2. A lilac coloured enteric-coated tablet containing 500 mg sodium valproate.
3. A red, cherry flavoured syrup containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; both presentations of tablet should be swallowed whole, if necessary with a little water, but not aerated water. It is recommended that the 200 mg tablet be used until the patient is stabilised; Epilim 500 enteric-coated is recommended for patients requiring high dosages, once the optimum dosage has been established.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,600 mg/day, or one other antiepileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined-dose level, and it may be found possible to maintain control with Epilim alone.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, this may be increased up to 50 mg/kg/day.

A dose of 50 mg/kg should be exceeded only in patients in whom plasma levels are measured. Plasma levels of 200 µg/ml should be exceeded only with caution, and with monitoring of haematological function.

Once known enzyme-inducers (e.g. phenobarbitone or primidone) have been withdrawn, or if side-effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of Epilim. A method of measuring plasma levels is available, should this be considered helpful; however, optimum dosage must ultimately be determined by seizure-control.

Contra-indications, warnings, etc There are no absolute contra-indications, but the following precautions should be noted.

Adverse reactions: No renal or cardiac effects attributable to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to Epilim 500 enteric-coated. Should symptoms persist, they can be relieved by standard medication.

Transient hair loss has been noted in some patients. Tremor has occasionally been observed at high dosage, which may be controlled by reduction of dosage. Reversible prolongation of bleeding time, sometimes with thrombocytopenia, has occurred, rarely, at high dosages. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery.

Isolated instances of disturbed liver function and jaundice have been reported within the first six months of treatment. If this occurs, Epilim should be withdrawn immediately. It is recommended that liver function be monitored before treatment with Epilim is started and then at intervals of two months for the first six months.

Combined medication: Epilim is generally well tolerated in combination with other antiepileptic agents; however, owing to the interaction known to occur between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anticonvulsant therapy. If the sedative effects of barbiturates are found to be enhanced, dosage of these compounds should be reduced. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors (MAOI) and other antidepressants, and dosage of such compounds should therefore also be reduced.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Overdosage: Few cases of accidental overdosage have been reported; recovery after ingestion of up to 30 g has been uneventful, with conservative management.

Epilim is absorbed very rapidly, so gastric lavage may be of limited value. However, as it is excreted almost entirely within 24 hours (70% in the urine), general supportive measures are recommended, with special attention to maintaining an adequate urinary output.

Women of childbearing age: Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil

until taken; they should be stored in a cool, dry place. Epilim Syrup should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP. The diluted product will have a 14-day shelf life.

Legal category POM.

Package quantities Epilim Tablets and Epilim 500 Enteric-coated Tablets are both packed in foil, in cartons of 100 tablets. Epilim Syrup is packed in 200 ml bottles.

Further information Epilim represents a new approach in the therapy of epilepsy. Its simple chemical structure, free from nitrogen, differs widely from that of other currently available anticonvulsant drugs, and biological studies suggest that it may have a different mode of action, producing an increase in the level of gamma-aminobutyric acid (GABA) in the brain. Although there is no simple correlation between GABA and convulsive activity, evidence linking them is growing. Epilim is clinically effective in the treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

References: Jeavons, P. M. & Clark, J. E. (1974): *Brit. med. J.* **2,** 584–6.
Barnes, S. E. & Bower, B. D. (1975): *Develop. Med Child Neurol.* **17,** 175–81.
Richens, A. & Ahmad, S. (1975): *Brit. med. J.* **4,** 255–6.
Haigh, D. & Forsythe, W. I. (1975): *Develop. Med. Child Neurol.* **17,** 743–8.
Jeavons, P. M., Clark, J. E. & Maheshwari, M. C. (1977): *Develop. Med. Child. Neurol.* **19,** 9–25.
'Clinical & Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy' (Proceedings of a symposium held at Nottingham University, Sept. 1975), MCS Consultants, England, 1976.

Product licence numbers

Epilim Tablets	0623/0001
Epilim 500 Enteric-coated Tablets	0623/0005
Epilim Syrup	0623/0004

**Trade Mark*

1979-80

Reckitt-Labaz
Reckitt & Colman Pharmaceutical Division
Dansom Lane
Hull HU8 7DS

EPILIM® ▽

Presentation 1. A white scored tablet containing 200 mg sodium valproate.

2. A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.

3. A red, cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; both presentations of tablet should be swallowed whole, if necessary with a little water, but not aerated water. It is recommended that the 200 mg tablet be used until the patient is stabilised; Epilim 500 enteric-coated is recommended for patients requiring high dosages, once the optimum dosage has been established.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,600 mg/day, or one other antiepileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined-dose level, and it may be found possible to maintain control with Epilim alone.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, this may be increased up to 50 mg/kg/day.

A dose of 50 mg/kg should be exceeded only in patients in whom plasma levels are measured. Plasma levels of 200 µg/ml should be exceeded only with caution, and with monitoring of haematological function.

Once known enzyme-inducers (e.g. phenobarbitone or primidone) have been withdrawn, or if side-effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of Epilim. A method of measuring plasma levels is available, should this be considered helpful; however, optimum dosage must ultimately be determined by seizure-control.

Contra-indications, warnings, etc There are no absolute contra-indications, but the following precautions should be noted.

Adverse reactions: No renal or cardiac effects attributable to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to Epilim 500 enteric-coated. Should symptoms persist, they can be relieved by standard medication.

Transient hair loss has been noted in some patients. Tremor has occasionally been observed at high dosage, which may be controlled by reduction of dosage. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but these usually been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery.

Isolated instances of disturbed liver function and jaundice have been reported within the first six months of treatment. If this occurs, Epilim should be withdrawn immediately. It is recommended that liver function be monitored before treatment with Epilim is started and then at intervals of two months for the first six months.

Combined medication: Epilim is generally well tolerated in combination with other antiepileptic agents, however, owing to the interaction known to exist between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anticonvulsant therapy. If the sedative effects of barbiturates are found to be enhanced, dosage of these compounds should be reduced. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors (MAOI) and other antidepressants, and dosage of such compounds should therefore also be reduced.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies. This may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Overdosage: Few cases of accidental overdosage have been reported; recovery after ingestion of up to 30 g has been uneventful, with conservative management.

Epilim is absorbed very rapidly, so gastric lavage may be of limited value. However, as it is excreted almost entirely within 24 hours (70% in the urine), general supportive measures are recommended, with special attention to maintaining an adequate urine output.

Women of childbearing age: Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of childbearing age the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil

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Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrups containing SO_2 as a preservative should be avoided. The diluted product will have a 14-day shelf-life.

Legal category POM.

Package quantities Epilim Tablets and Epilim 500 Enteric-coated Tablets are both packed in 1pt. in cartons of 100 tablets. Epilim Syrup is packed in 200 ml bottles.

Further information Epilim represents a new approach in the therapy of epilepsy. Its simple chemical structure, free from nitrogen, differs widely from that of other currently available anticonvulsant drugs, and biological studies suggest that it may have a different mode of action, producing an increase in the level of gamma-aminobutyric acid (GABA) in the brain. Although there is no simple correlation between GABA and convulsive activity, evidence linking them is growing. Epilim is clinically effective in the treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

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Barnes, S. E. & Bower, B. D. (1975): *Develop. Med. Child Neurol.* **17**, 175–81.
Richens, A. & Ahmad, S. (1975): *Brit. med. J.* **4**, 555–6.
Singh, D. & Forsythe, W. I. (1975): *Develop. Med. Child Neurol.* **17**, 743–8.
Jeavons, P. M., Clark, J. E. & Maheshwari, M. C. (1977): *Develop. Med. Child. Neurol.* **19**, 9–25.
'Clinical & Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy' (Proceedings of a symposium held at Nottingham University, Sept. 1975). MCS Consultants, England, 1976.

Product licence numbers

Epilim Tablets	0623/0001
Epilim 500 Enteric-coated Tablets	0623/0005
Epilim Syrup	0623/0004

**Trade Mark*

1980-81

Reckitt-Labaz
Reckitt & Colman Pharmaceutical Division
Dansom Lane
Hull HU8 7DS

EPILIM®

Presentation 1. A white scored tablet containing 200 mg sodium valproate.

2. A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.

3. A red, cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; both presentations of tablet should be swallowed whole, if necessary with a little water, but not aerated water. It is recommended that the 200 mg tablet be used until the patient is stabilised; Epilim 500 enteric-coated is recommended for patients requiring high dosages, once the optimum dosage has been established.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,600 mg/day, or one other antiepileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined-dose level, and it may be found possible to maintain control with Epilim alone.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, this may be increased up to 50 mg/kg/day.

A dose of 50 mg/kg should be exceeded only in patients in whom plasma levels are measured. Plasma levels of 200 µg/ml should be exceeded only with caution, and with monitoring of haematological function.

Once known enzyme-inducers (e.g. phenobarbitone or primidone) have been withdrawn, it may be possible to maintain seizure control on a reduced dose of Epilim. A method of measuring plasma levels is available, should this be considered helpful; however, optimum dosage must ultimately be determined by seizure-control.

Contra-indications, warnings, etc There are no absolute contra-indications, but the following precautions should be noted.

Side-effects: No cardiac effects attributable to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to Epilim 500 enteric-coated. Should symptoms persist, they can be relieved by standard medication.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but have usually been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in a few patients whose treatment included Epilim. These incidents occurred during the early months of treatment. Although a causal relationship has not been established, it is recommended that liver function be investigated prior to commencing therapy and monitored at two-monthly intervals thereafter for up to six months. Should liver dysfunction be suspected, immediate withdrawal of the drug is indicated, prior to full investigation of the possible causes. Caution should be exercised when administering Epilim to patients with pre-existing liver disease.

Combined medication: Epilim is generally well tolerated in combination with other antiepileptic agents; however, owing to the interaction known to occur between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anticonvulsant therapy. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors (MAOI) and other antidepressants, and dosage of such compounds should therefore also be reduced.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Overdosage: Few cases of accidental overdosage have been reported; recovery after ingestion of up to 30 g has been uneventful, with conservative management.

Epilim is absorbed very rapidly, so gastric lavage may be of limited value. However, as it is excreted almost entirely within 24 hours (70% in the urine), general supportive measures are recommended, with special attention to maintaining an adequate urinary output.

Women of childbearing age: Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a cool, dry place. Epilim Syrup should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should be avoided. The diluted product will have a 14-day shelf-life.

Legal category POM.

Package quantities Epilim Tablets and Epilim 500 Enteric-coated Tablets are both packed in foil, in cartons of 100 tablets. Epilim Syrup is packed in 200 ml bottles.

Further information Nil.

Product licence numbers

Epilim Tablets	0623/0001
Epilim 500 Enteric-coated Tablets	0623/0005
Epilim Syrup	0623/0004

*Trade Mark

1982-83.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by the drug.

The electrophysiological properties of Corderone X may be summarised as follows:

1. Prolongation without flattening of the action potential in atrial and ventricular muscle and, to a lesser extent, in Purkinje fibres, without change in the resting membrane potential. (Class III activity – Singh and Vaughan Williams).
2. Reduction in the maximum rate of repolarization.
3. Marked antifibrillatory action.
4. No significant depression of spontaneous diastolic depolarization of the His-Purkinje fibres.
5. Lengthening the refractory period of the myocardium and conducting system, including accessory pathways.

This electrophysiological profile explains the marked efficacy of Corderone X in the treatment of arrhythmias where the refractory period of the accessory pathway is very short.

Product licence number 0623/0007.

EPILIM®

Presentation

1. *Epilim 200 enteric-coated:* A lilac-coloured enteric-coated tablet containing 200 mg sodium valproate.
2. *Epilim tablets:* A white, scored tablet containing 200 mg sodium valproate.
3. *Epilim 500 enteric-coated:* A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.
4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; enteric-coated and plain tablets should be swallowed whole, if necessary with a little water, but not aerated water. It is recommended that optimum dosage be established using the 200 mg enteric-coated tablet. Epilim 500 enteric-coated is recommended for patients requiring high dosages.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,600 mg/day, or one other anti-epileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined-dose level, and it may be found possible to maintain control with Epilim alone.

In sole therapy the dose/plasma level ratio is between 1:2.5–3 in children, and 1:3.5–4 in adults. In combination therapy the ratios are reduced to 1:1.2–1.5 in children, and 1:2.1–2.4 in adults. Therefore when added to existing therapy higher doses of Epilim may be required to maintain therapeutic plasma levels than when it is used as sole therapy. Conversely, when changing from combined therapy to sole therapy a dosage reduction of Epilim may be required.

Once known enzyme-inducers (e.g. phenytoin, phenobarbitone, carbamazepine) have been withdrawn, it may be possible to maintain seizure control on a reduced dose of Epilim. A method of measuring plasma levels is available, should this be considered helpful; however, optimum dosage must ultimately be determined by seizure-control.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, this may be increased up to 50 mg/kg/day but should be undertaken only in patients in whom plasma valproate levels, clinical chemistry and haematological parameters can be monitored.

Contra-indications, warnings, etc Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks. No deaths have occurred in patients receiving the drug continuously for more than 6 months.

Biochemical tests may not always become abnormal early in the evolution of hepatic failure; non specific findings such as loss of seizure control, malaise, anorexia and vomiting, developing after a period of satisfactory Epilim treatment may alert the clinician to the possibility of hepatic damage.

Epilim should not be administered to patients with pre-existing hepatic dysfunction.

All patients for whom treatment with Epilim is contemplated should have base line liver function assessed (including serum fibrinogen and albumin levels) prior to commencement of therapy. Liver function should be carefully monitored, particularly during the first six months of therapy, and when dosage is being titrated upwards.

Patients with a prior history of liver disease or with severe or unusual seizure disorders, e.g. those accompanied by mental retardation and/or organic brain disease, should be followed particularly carefully. Transient elevations of liver enzymes are not uncommon during early treatment with Epilim. However, if liver enzymes elevations are accompanied by other evidence of hepatic dysfunction, especially raised serum bilirubin or lowered serum fibrinogen, then the drug should be immediately withdrawn.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. It has been suggested that this may be related to interference with propionic acid metabolism. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, Epilim should be discontinued.

Valproic acid inhibits second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but have usually

been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported with sodium valproate. The blood picture returned to normal when the drug was discontinued.

There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate. Patients experiencing acute abdominal pain should have the serum amylase estimated.

No cardiac effects attributed to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to the Epilim enteric-coated formulations.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported. Increase in alertness, appetite and weight may occur.

Combined medication: Epilim is generally well tolerated in combination with other anti-epileptic agents; however owing to the interaction known to occur between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anti-convulsant therapy. Epilim may block the metabolism of barbiturates giving rise to raised plasma barbiturate level. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors and other anti-depressants, and dosage of such compounds should, therefore, also be reduced. Epilim does not induce liver enzymes, and there have been no reports of loss of efficacy of oral contraceptive agents.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Women of childbearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Overdosage: Nine cases of accidental and fourteen cases of suicidal overdosage have been reported. Full recovery occurred in 22 following treatment which included induced vomiting, gastric lavage, assisted ventilation, forced diuresis and other supportive measures; naloxone was used successfully in one patient.

The only known fatality followed a massive suicidal overdose resulting in a plasma level of 1970 mg/litre.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a cool, dry place. Epilim Syrup should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14-day shelf-life.

Legal category POM.

Package quantities Epilim tablets, Epilim 200 enteric-coated and Epilim 500 enteric-coated tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup is packed in 200 ml bottles.

Further information Although the beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels, anticonvulsant activity may be optimal when the percentage of free drug in the plasma is 9–15% of the total level. Above this range an increase in the percentage of the free drug may be associated with a higher incidence of adverse effects.

When plasma valproic acid is within the recommended range of 50–120 mg/litre (350–840 m mol/litre) and serum albumin levels are normal, about 90% of the drug is bound to albumin. If the total plasma valproic acid rises above the upper range of normal, or if there is hypoalbuminaemia, the percentage of free valproic acid may rise markedly and in disproportion to any dosage increase.

Facilities for the direct measurement of free valproic acid levels are not readily available, however the amounts of bound and free drug may be calculated approximately by assuming that 1 gram of serum albumin will bind 2 mg of valproate (maximum binding 90%).

Product licence numbers

Epilim 200 enteric-coated tablets	0623/0006
Epilim Tablets	0623/0001
Epilim 500 enteric-coated tablets	0623/0005
Epilim Syrup	0623/0004

**Trade Mark*

drug, a maintenance dose of only one tablet/day, or less, is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by the drug.

The electrophysiological properties of Cordarone X may be summarised as follows:

1. Prolongation without flattening of the action potential in atrial and ventricular muscle and, to a lesser extent, in Purkinje fibres, without change in the resting membrane potential. (Class III activity – Singh and Vaughan Williams).
2. Reduction in the maximum rate of repolarization.
3. Marked antifibrillatory action.
4. No significant depression of spontaneous diastolic depolarization of the His-Purkinje fibres.
5. Lengthening the refractory period of the myocardium and conducting system, including accessory pathways.

This electrophysiological profile explains the marked efficacy of Cordarone X in the treatment of arrhythmias where the refractory period of the accessory pathway is very short.

Product licence number 0823/0007.

1983 – 84

Pg 1

EPILIM®

Presentation

1. *Epilim 200 enteric-coated:* A lilac-coloured enteric-coated tablet containing 200 mg sodium valproate.
2. *Epilim 500 enteric-coated:* A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.
3. *Epilim Syrup:* A red cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.
4. *Epilim tablets:* A white scored tablet containing 200 mg sodium valproate.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Epilim should preferably be taken with or after food; enteric-coated and plain tablets should be swallowed whole, if necessary with a little water, but not aerated water. It is recommended that optimum dosage be established using the 200 mg enteric-coated tablet. Epilim 500 enteric-coated is recommended for patients requiring high dosages.

Adults: Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000–1,600 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,600 mg/day, or one other anti-epileptic agent may be added, at a low dosage.

In patients already receiving other therapy the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined dose.

level, and it may be found possible to maintain control with Epilim alone.

In sole therapy the dose/plasma level ratio is between 1:2.5–3 in children, and 1:3.5–4 in adults. In combination therapy the ratios are reduced to 1:1.2–1.5 in children, and 1:2.1–2.4 in adults. Therefore when added to existing therapy higher doses of Epilim may be required to maintain therapeutic plasma levels than when it is used as sole therapy. Conversely, when changing from combined therapy to sole therapy a dosage reduction of Epilim may be required.

Once known enzyme-inducers (e.g. phenytoin, phenobarbitone, carbamazepine) have been withdrawn, it may be possible to maintain seizure control on a reduced dose of Epilim. A method of measuring plasma levels is available, should this be considered helpful; however, optimum dosage must ultimately be determined by seizure-control.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) in divided doses, with spaced increases until control is achieved: this is usually within the range 20–30 mg/kg of body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases, this may be increased up to 30 mg/kg/day but should be undertaken only in patients in whom plasma valproate levels, clinical chemistry and haematological parameters can be monitored.

Contra-indications, warnings, etc Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks.

Biochemical tests may not always become abnormal early in the evolution of hepatic failure; non specific findings such as loss of seizure control, malaise, anorexia and vomiting, developing after a period of satisfactory Epilim treatment may alert the clinician to the possibility of hepatic damage.

Epilim should not be administered to patients with pre-existing hepatic dysfunction.

All patients for whom treatment with Epilim is contemplated should have base line liver function assessed (including serum fibrinogen and albumin levels) prior to commencement of therapy. Liver function should be carefully monitored, particularly during the first six months of therapy, and when dosage is being titrated upwards.

Patients with a prior history of liver disease or with severe or unusual seizure disorders, e.g. those accompanied by mental retardation and/or organic brain disease, should be followed particularly carefully. Transient elevations of liver enzymes are not uncommon during early treatment with Epilim. However, if liver enzyme elevations are accompanied by other evidence of hepatic dysfunction, especially raised serum bilirubin or lowered serum fibrinogen, then the drug should be immediately withdrawn.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. It has been suggested that this may be related to interference with propionic acid metabolism. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, Epilim should be discontinued.

Valproic acid inhibits second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but have usually been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported with sodium valproate. The blood picture returned to normal when the drug was discontinued.

There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate. Patients experiencing acute abdominal pain should have the serum amylase estimated.

No cardiac effects attributed to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to the Epilim enteric-coated formulations.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported. Increase in alertness, appetite and weight may occur.

Combined medication: Epilim is generally well tolerated in combination with other anti-epileptic agents; however owing to the interaction known to occur between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anti-convulsant therapy. Epilim may block the metabolism of barbiturates giving rise to raised plasma barbiturate level. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors and other anti-depressants, and dosage of such compounds should, therefore, also be reduced. Epilim does not induce liver enzymes, and there have been no reports of loss of efficacy of oral contraceptive agents.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

Women of childbearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Overdosage Nine cases of accidental and fourteen cases of suicidal overdosage have been reported. Full recovery occurred in 22 following treatment which included induced vomiting, gastric lavage, assisted ventilation, forced diuresis and other supportive measures; naloxone was used successfully in one patient.

The only known fatality followed a massive suicidal overdose resulting in a plasma level of 1970 mg/litre.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a cool, dry place. Epilim Syrup should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14-day shelf-life.

Legal category POM.

Package quantities Epilim tablets, Epilim 200 enteric-coated and Epilim 500 enteric-coated tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup is packed in 200 ml bottles.

Further information Although the beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels, anticonvulsant activity may be optimal when the percentage of free drug in the plasma is 9–15% of the total level. Above this range an increase in the percentage of the free drug may be associated with a higher incidence of adverse effects.

When plasma valproic acid is within the recommended range of 50–120 mg/litre (350–840 mcg mol/litre) and serum albumin levels are normal, about 90% of the drug is bound to albumin. If the total plasma valproic acid rises above the upper range of normal, or if there is hypoalbuminaemia, the percentage of free valproic acid may rise markedly and in disproportion to any dosage increase.

Facilities for the direct measurement of free valproic acid levels are not readily available, however the amounts of bound and free drug may be calculated approximately by assuming that 1 gram of serum albumin will bind 2 mg of valproate (maximum binding 90%).

Product licence numbers

Epilim 200 enteric-coated tablets	0623/0006
Epilim 500 enteric-coated tablets	0623/0005
Epilim Syrup	0623/0004
Epilim Tablets	0623/0001

OSSOPAN*

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base. Ossopan powder is pale brown, granular, with an aromatic odour. Each gram of powder contains 820 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Ossopan tablets are yellow, sugar-coated. Each tablet contains 200 mg MCHC, providing 43 mg calcium and 20 mg phosphorus.

Uses Provision of calcium and phosphorus in all defects of skeletal metabolism, including:

(i) most forms of osteoporosis with or without corticosteroid therapy;
(ii) osteogenesis imperfecta;
(iii) rickets and osteomalacia;
(iv) fractures and conditions requiring orthopaedic surgery; and
(v) dental conditions associated with mineral disturbances.

Dosage and administration *Ossopan powder:* One to two level 5 ml spoonfuls daily in divided doses with or before food.

Ossopan tablets: Up to 16 tablets daily, to be taken in divided doses, before meals.

Contra-indications, warnings, etc *Contra-indications:* Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calculus stone formation.

Pharmaceutical precautions Store in a cool, dry place.

Legal category P.

Package quantities *Ossopan powder:* jars containing 50 grams.
Ossopan tablets: packs of 150 and 1,000.

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite, and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest the MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers
Ossopan powder: 0376/5001
Ossopan tablets: 0376/5000.

**Trade Mark*

is incompatible with saline and should be administered solely in 5% Dextrose solution.

Legal category POM.

Package quantities *Tablets:* carton of 30 tablets (in blister pack of 10 tablets).
Intravenous injection: carton of 10 ampoules.

Further information Cordarone X Intravenous may be used prior to DC cardioversion. It has been used to treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X is strongly protein bound and its pharmacokinetic and pharmacodynamic half-lives are both very long, of the order of 14–28 days. High dose oral Cordarone X, usually 3 tablets/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half life of the drug, a maintenance dose of only 1 tablet/day, or less, is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by the drug.

The electrophysiological properties of Cordarone X may be summarised as follows:

1. Prolongation without flattening of the action potential in atrial and ventricular muscle and, to a lesser extent, in Purkinje fibres, without change in the resting membrane potential. (Class III activity – Singh and Vaughan Williams).
2. Reduction in the maximum rate of repolarization.
3. Marked antifibrillatory action.
4. No significant depression of spontaneous diastolic depolarization of the His-Purkinje fibres.
5. Lengthening the refractory period of the myocardium and conduction system, including accessory pathways.

This electrophysiological profile explains the marked efficacy of Cordarone X in the treatment of arrhythmias where the refractory period of the accessory pathway is very short.

Product licence number

Cordarone X	0623/0007
Cordarone X Intravenous	0623/0012

EPILIM®

Presentation

1. *Epilim 200 mg Enteric-Coated tablets:* A lilac-coloured enteric-coated tablet containing 200 mg sodium valproate.
2. *Epilim 500 mg Enteric-Coated tablets:* A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.
3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg sodium valproate.
4. *Epilim Syrup:* A red cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.
5. *Epilim Liquid:* A red cherry-flavoured, sugar-free liquid containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age Epilim should be

used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased up to 40 mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

The tablets may be given twice daily. Uncoated tablets may be crushed if necessary. Epilim Syrup and Liquid should be given in divided doses.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, e.g. patients with a prior history of liver disease, children with severe epilepsy associated with mental retardation or structural brain damage or metabolic disorder, and such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and test of liver function should be monitored until they return to normal.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim with or after food.

Increase in alertness and appetite may occur and an increase in weight is not uncommon.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monamine oxidase inhibitors and other anti-depressants. Epilim does not induce liver enzymes, and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml, Epilim Liquid is, however, sugar-free.

Women of childbearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim.

Overdosage: Cases of accidental and suicidal overdosage have been reported. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, forced diuresis and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until

taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 mg enteric-coated, Epilim 500 mg enteric-coated tablets and Epilim 100 mg crushable tablets are packed in foil, in cartons of 100 tablets.
Epilim Syrup and Epilim Liquid are packed in 200 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 5% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 mg Enteric-Coated Tablets	0623/0005
Epilim 200 mg Enteric-Coated tablets	0623/0006
Epilim 100 mg Crushable Tablets	0623/0015
Epilim Liquid	0623/0016

OSSOPAN*

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base. Ossopan powder is pale brown, granular, with an aromatic odour. Each gram of powder contains 820 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Ossopan tablets are yellow, sugar-coated. Each tablet contains 200 mg MCHC, providing 43 mg calcium and 20 mg phosphorus.

Uses Provision of calcium and phosphorus in all defects of skeletal metabolism, including:
(i) most forms of osteoporosis with or without corticosteroid therapy;
(ii) osteogenesis imperfecta;
(iii) rickets and osteomalacia;
(iv) fractures and conditions requiring orthopaedic surgery; and
(v) dental conditions associated with mineral disturbances.

Dosage and administration *Ossopan powder:* One to two level 5 ml spoonfuls daily in divided doses with or before food.

Ossopan tablets: Up to 16 tablets daily, to be taken in divided doses, before meals.

Contra-indications, warnings, etc *Contra-indications:* Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Pharmaceutical precautions Store in a cool, dry place.

Legal category P.

Package quantities *Ossopan powder:* jars containing 50 grams.
Ossopan tablets: packs of 150 and 1,000.

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite, and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest that MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers
Ossopan powder: 0376/5001
Ossopan tablets: 0376/5000.

**Trade Mark*

treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X is strongly protein bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half life of more than 100 days has been reported. High doses of Cordarone X, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half life of the drug, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

Product licence numbers

Cordarone X 100	0623/0017
Cordarone X 200	0623/0007
Cordarone X Intravenous	0623/0012

EPILIM*

Presentation

1. *Epilim 200 mg Enteric-Coated tablets:* A lilac-coloured enteric-coated tablet containing 200 mg sodium valproate.

2. *Epilim 500 mg Enteric-Coated tablets:* A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg sodium valproate.

4. *Epilim Syrup:* A red cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.

5. *Epilim Liquid:* A red cherry-flavoured, sugar-free liquid containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, focal or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased up to 40 mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased serum albumin the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: The tablets may be given twice daily. Uncoated tablets may be crushed if necessary, or the Syrup and Liquid should be given in divided doses.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish whether, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, e.g. patients with a prior history of liver disease, children with severe epilepsy associated with mental retardation or structural brain damage or metabolic disorder, and such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but

usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these probems can usually be overcome by administering Epilim with or after food.

Increase in alertness and appetite may occur and an increase in weight is not uncommon.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monamine oxidase inhibitors and other anti-depressants. Epilim does not induce liver enzymes, and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml. Epilim Liquid is, however, sugar-free.

Women of childbearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of the maternal plasma levels. Thus there appears to be no specific indication to breast feeding by patients on Epilim.

Overdosage: Cases of accidental and suicidal overdosage have been reported. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, forced diuresis and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 mg enteric-coated, Epilim 500 mg enteric-coated tablets and Epilim 100 mg crushable tablets are packed in foil, in cartons of 100 tablets.

Epilim Syrup and Epilim Liquid are packed in 200 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 mg Enteric-Coated Tablets	0623/0005
Epilim 200 mg Enteric-Coated Tablets	0623/0006
Epilim 100 mg Crushable Tablets	0623/0015
Epilim Liquid	0623/0016

OSSOPAN®

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base.

Ossopan 800 tablets are pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan powder is pale brown, granular, with an aromatic odour. Each gram contains 820 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Ossopan 200 tablets are yellow, sugar-coated. Each tablet contains 200 mg MCHC, providing 43 mg calcium and 20 mg phosphorus.

Uses Provision of calcium and phosphorus in osteoporosis, rickets and osteomalacia.

Dosage and administration

Ossopan 800: 4–8 tablets to be taken daily in divided doses, before meals.

Ossopan powder: One to two level 5 ml spoonfuls daily in divided doses with or before food.

Ossopan 200: 16–32 tablets daily, to be taken in divided doses, before meals.

Use in the elderly: There are no special dosage recommendations.

Contra-indications, warnings, etc

Contra-indications: Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Treatment of overdosage: No cases of intoxication with Ossopan due to deliberate or accidental overdosage have been reported to the Company. It is considered overdosage is unlikely to be a problem.

Pharmaceutical precautions Store in a cool, dry place.

Legal category P.

Package quantities

Ossopan powder: jars containing 50 grams.
Ossopan 200: packs of 150 and 1,000 tablets.
Ossopan 800: packs of 50 tablets.

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite and

should be protected from light. Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% Dextrose solution.

Legal category POM.

Package quantities *Tablets:* carton of 30 tablets (in blister pack of 10 tablets).
Intravenous injection: carton of 10 ampoules.

Further information Cordarone X Intravenous may be used prior to DC cardioversion. It has been used to treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X is strongly protein-bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half-life of more than 100 days has been reported. High doses of Cordarone X, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the drug, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

Product licence numbers

Cordarone X 100	0823/0017
Cordarone X 200	0823/0007
Cordarone X Intravenous	0823/0012

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing Cosbiol (Squalene) 3.0%, hexachlorophane 0.5%, allantoin 0.25%.

Uses Prevention of pressure sores. Prevention and treatment of incontinence rash and non-specific rashes. Skin antiseptic for preparation of split-skin donor areas. As a hand cream for medical and surgical staff to reduce the risk of cross infection.

Dosage and administration Apply sparingly as a routine procedure every 4 to 6 hours and after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Contra-indications, warnings, etc Dermalex skin lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex should not be administered except on medical advice to children under two years of age.

Pharmaceutical precautions No special storage requirements.

Legal category P.

Package quantities 100 mls: Community nursing pack: '1 patient for 4 weeks'. 250 mls: Ward pack '10 patients for 7 days' (Pump action dispenser available for this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It maintains its deep antiseptic activity in the skin for at least six hours, and in addition Cosbiol provides a beneficial effect for patients with dry skin.

Product licence number 1983/5000.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg sodium valproate.
2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg sodium valproate.
3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg sodium valproate.
4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg sodium valproate per 5 ml.
5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg sodium valproate per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased up to 40 mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have

been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indication: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, e.g. patients with a prior history of liver disease, children with severe epilepsy associated with mental retardation or structural brain damage or metabolic disorder, and such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: Valproic acid and sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There are no known contra-indications to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including

induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 200 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg crushable tablets	0623/0015
Epilim Liquid	0623/0016

OSSOPAN*

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base.

Ossopan 800 tablets are pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan powder is pale brown, granular, with an aromatic odour. Each gram contains 920 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Uses Provision of calcium and phosphorus in osteoporosis, rickets and osteomalacia.

Dosage and administration

Ossopan 800: 4–8 tablets to be taken daily in divided doses, before meals.

Ossopan powder: One to two level 5 ml spoonfuls daily in divided doses with or before food.

Use in the elderly: There are no special dosage recommendations.

Contra-indications, warnings, etc

Contra-indications: Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Treatment of overdosage: No cases of intoxication with Ossopan due to deliberate or accidental overdosage have been reported to the Company. It is considered that overdosage is unlikely to be a problem.

Pharmaceutical precautions Store in a cool dry place.

Legal category P.

Package quantities
Ossopan 800: packs of 60 tablets.
Ossopan powder: jars containing 50 grams.

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest that MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers

Ossopan 800 tablets	0376/0001
Ossopan powder	0376/5001

TRIFYBA* ▽

Presentation Trifyba is a light brown fibrous powder, derived from the husk of wheat (Testa Triticum Tricum). The fibre consists of hemicellulose, cellulose, lignin and pectin. It is presented as single dose sachets containing 3.5 g or as bulk packs containing 250 g.

Uses Colonic and gastro-intestinal disorders where a high-fibre regimen is indicated including simple constipation, uncomplicated diverticular disease, irritable colon, haemorrhoidal disorders and fissures and also conditions where straining at stool should be avoided.

Dosage and administration

Adults: One sachet or 25 ml measure two to three times daily.

Children: Half to one sachet or a half to a full 25 ml measure once or twice daily depending on age and size.

Trifyba should be taken mixed with food or liquids. For maximum effect adequate fluids should be taken.

Use in the elderly: There are no special dosage recommendations for the elderly except that it is most important to ensure that their fluid intake is adequate.

Contra-indications, warnings, etc Trifyba is contra-indicated in cases of intestinal obstruction. Some patients may experience transient abdominal distention and flatulence, but this rapidly diminishes and usually disappears within two weeks.

Treatment of overdosage: Due to the nature of the preparation, overdosage is unlikely. If it does occur, it should be treated conservatively and the patient given copious fluids by mouth.

Pharmaceutical precautions Nil.

Legal category GSL.

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NOFI

Dermalex should not be administered except on medical advice to children under two years of age.

Pharmaceutical precautions No special storage requirements.

Legal category P.

Package quantities 100 mls.
250 mls (Pump action dispenser with this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It maintains its deep antiseptic activity in the skin for at least six hours, and in addition Cosbiol provides a beneficial effect for patients with dry skin.

Product licence number 1983/5000.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate BP.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate BP.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate BP.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate BP per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate BP per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased up to 40 mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indication: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: Valproic acid and sodium valproate, like certain other anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on Epilim

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The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 200 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

OSSOPAN*

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base.

Ossopan 800 tablets are pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan powder is pale brown, granular, with an aromatic odour. Each gram contains 820 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Uses Provision of calcium and phosphorus in osteoporosis, rickets, osteomalacia and during lactation.

Dosage and administration

Ossopan 800: 4–8 tablets to be taken daily in divided doses, before meals.

Ossopan powder: One to two level 5 ml spoonfuls daily in divided doses with or before food.

Use in the elderly: There are no special dosage recommendations.

Contra-indications, warnings, etc

Contra-indications: Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Treatment of overdosage: No cases of intoxication with Ossopan due to deliberate or accidental overdosage have been reported to the Company. It is considered that overdosage is unlikely to be a problem.

Pharmaceutical precautions Store in a cool, dry place.

Legal category P.

Package quantities
Ossopan 800: packs of 50 tablets.
Ossopan powder: jars containing 50 grams.

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest that MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers

Ossopan 800 tablets	0376/0001
Ossopan powder	0376/5001

**Trade Mark*

Treatment of overdosage: Animal studies indicate that Cordarone X has a high LD_{50}, hence it is most unlikely that a patient will ingest an acute toxic dose. In such an event gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia ensues beta-adrenostimulants or glucagon may be given.

Pharmaceutical precautions Tablets and ampoules should be protected from light. Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% Dextrose solution.

Legal category POM.

Package quantities *Tablets:* carton of 30 tablets (in blister pack of 10 tablets).
Intravenous injection: carton of 10 ampoules.

Further information Cordarone X Intravenous may be used prior to DC cardioversion. It has been used to treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X is strongly protein-bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half-life of more than 100 days has been reported. High doses of Cordarone X, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the drug, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

Product licence numbers

Cordarone X 100	0623/0017
Cordarone X 200	0623/0007
Cordarone X Intravenous	0623/0012

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing Cosbiol (Squalane) 3.0%, hexachlorophane 0.5%, allantoin 0.2%.

Uses Prevention of pressure sores. Prevention and treatment of incontinence rash and non-specific rashes. Skin antiseptic for preparation of split-skin donor areas. As a hand cream for medical and surgical staff to reduce the risk of cross infection.

Dosage and administration Apply sparingly as a routine procedure every 4 to 6 hours and after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Contra-indications, warnings, etc Dermalex skin lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex should not be administered except on medical advice to children under two years of age.

Pharmaceutical precautions No special storage requirements.

Legal category P.

Package quantities 100 mls.
250 mls (Pump action dispenser with this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It maintains its deep antiseptic activity in the skin for at least six hours, and in addition Cosbiol provides a beneficial effect for patients with dry skin.

Product licence number 1983/5000.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate BP.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate BP.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate BP.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate BP per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate BP per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased up to 40 mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of reduced binding to serum

albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-Indications, warnings, etc

Contra-indication: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: Valproic acid and sodium valproate, like certain other anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of

total maternal plasma levels. There appears to be no contra indication to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

EPILIM* INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate BP 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced if sedation is observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if

any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been reported occasionally and appear to be dose-related effects.

Sedation has been occasionally reported, usually in combination with other anticonvulsants. In Epilim monotherapy it occurs on rare occasions early in treatment and is usually transient. It is possible that rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations may occur.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: Some studies have demonstrated an increase in the expected incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated.

There is evidence of teratogenic effects with anticonvulsants including Epilim in animals and there have been reports of congenital abnormalities in offspring of a small number of epileptic patients receiving therapy during pregnancy.

In pregnancy, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: At plasma concentrations of up to 5 to 8 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2-8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack of one vial of 400 mg Sodium Valproate BP and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8 –20 hours.

Product licence numbers

Vial of freeze dried powder	0623/0038
Ampoule of solvent	0623/0040

OSSOPAN®

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which provides calcium, phosphorus and essential trace elements in a protein base.

Ossopan 800 tablets are pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan powder is pale brown, granular, with an aromatic odour. Each gram contains 820 mg MCHC, providing 176 mg calcium and 82 mg phosphorus. One level 5 ml spoonful contains approximately 4 grams.

Uses Provision of calcium and phosphorus in osteoporosis, rickets, osteomalacia and during lactation.

It may potentiate oral anticoagulant therapy. Consideration should be given to the possibility that Cordarone X may alter the plasma concentrations of other drugs particularly those which are highly protein-bound e.g. phenytoin.

Cordarone X should be used with caution in combination with beta-blocking agents or calcium antagonists, as any tendency to produce bradycardia may be potentiated.

Women of child-bearing age: Although no teratogenic effects have been observed in animals, there are insufficient data on the use of Cordarone X during pregnancy in humans to judge any possible toxicity.

Breast-feeding: Cordarone X is present in the breast milk in significant quantities and breast-feeding is contra-indicated.

Treatment of overdosage: Animal studies indicate that Cordarone X has a high LD_{50}, hence it is most unlikely that a patient will ingest an acute toxic dose. In such an event gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia ensues beta-adrenostimulants or glucagon may be given.

Pharmaceutical precautions Tablets and ampoules should be protected from light. Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% Dextrose solution.

Legal category POM.

Package quantities *Tablets:* carton of 28 tablets (in blister pack of 14 tablets) (OP).
Intravenous injection: carton of 10 ampoules.

Further information Cordarone X Intravenous may be used prior to DC cardioversion. It has been used to treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X is strongly protein-bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half-life of more than 100 days has been reported. High doses of Cordarone X, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the drug, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

Product licence numbers

Cordarone X 100	0623/0017
Cordarone X 200	0623/0007
Cordarone X Intravenous	0623/0012

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing Cosbiol (Squalane) 3.0%, hexachlorophane 0.5%, allantoin 0.2%.

Uses Prevention of pressure sores. Prevention and treatment of incontinence rash and non-specific rashes. Skin antiseptic for preparation of split-skin donor areas. As a hand cream for medical and surgical staff to reduce the risk of cross infection.

Dosage and administration Apply sparingly as a routine procedure every 4 to 6 hours and after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Contra-indications, warnings, etc Dermalex skin lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex should not be administered except on medical advice to children under two years of age.

Pharmaceutical precautions No special storage requirements.

Legal category P.

Package quantities 100 mls (OP).
250 mls (Pump action dispenser with this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It maintains its deep antiseptic activity in the skin for at least six hours, and in addition Cosbiol provides a beneficial effect for patients with dry skin.

Product licence number 1983/5000.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate BP.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate BP.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate BP.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate BP per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate BP per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/

day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indication: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been reported rarely.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant

properties (e.g. warfarin and aspirin). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated.

There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

EPILIM* INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate BP 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections).

Uses. Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have

been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced if sedation is observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been reported occasionally and appear to be dose-related effects.

Sedation has been occasionally reported, usually in combination with other anticonvulsants. In Epilim monotherapy it occurs on rare occasions early in treatment and is usually transient. It is possible that rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations may occur.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and aspirin). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated.

There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C, infusion solutions at 2–8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack of one vial of 400 mg Sodium Valproate BP and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8–20 hours.

Product licence numbers

Vial of freeze dried powder	0623/0038
Ampoule of solvent	0623/0040

OSSOPAN*

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which is a source of calcium and phosphorus in a protein base containing trace elements.

Ossopan 800 tablets: Pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan granules: Coarse, brown granules, with a taste and odour of malt and cocoa. Each sachet contains 3320 mg MCHC, providing 712 mg calcium and 332 mg phosphorus. Each sachet contains approximately 4 grams, equivalent to 4 Ossopan 800 tablets.

Uses Provision of calcium and phosphorus in osteoporosis, rickets, osteomalacia and during lactation.

Dosage and administration

Ossopan 800: 4–8 tablets to be taken daily in divided doses, before meals.

Ossopan granules: One to two sachets daily with or before food.

Use in the elderly: There are no special dosage recommendations.

Contra-indications, warnings, etc

Contra-indications: Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Treatment of overdosage: No cases of intoxication with Ossopan due to deliberate or accidental overdosage have been reported to the Company. It is considered that overdosage is unlikely to be a problem.

Pharmaceutical precautions Store in a dry place.

Legal category P.

Package quantities

Ossopan 800: packs of 50 tablets.

Ossopan granules: packs containing 28 sachets (OP).

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest that MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers

Ossopan 800 tablets	0376/0001
Ossopan granules	0623/0045

**Trade Mark*

cient data on the use of Cordarone X during pregnancy in humans to judge any possible toxicity. However, in view of the pharmacological properties of the drug on the foetus and its effect on the foetal thyroid gland, its administration in pregnancy should be avoided.

Breast-feeding: Cordarone X is present in the breast milk in significant quantities and breast-feeding is contra-indicated.

Treatment of overdosage: Animal studies indicate that Cordarone X has a high LD_{50}, hence it is most unlikely that a patient will ingest an acute toxic dose. In such an event gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia ensues beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of Cordarone X, adequate and prolonged surveillance of the patient, particularly cardiac status is recommended.

Pharmaceutical precautions Tablets and ampoules should be protected from light. Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% Dextrose solution. Solutions containing less than 2 ampoules Cordarone X Intravenous in 500 ml Dextrose 5% are unstable and should not be used.

Legal category POM.

Package quantities *Tablets:* carton of 28 tablets (in blister pack of 14 tablets) (OP).
Intravenous injection: carton of 10 ampoules.

Further information Cordarone X Intravenous may be used prior to DC cardioversion. It has been used to treat successfully atrial, junctional and ventricular tachyarrhythmias. It may be used where a rapid response is required, such as following a myocardial infarction.

Cordarone X induces ECG changes; QT interval lengthening corresponding to prolonged repolarisation; U and deformed T waves may occur because of the fixing of amiodarone in myocardial tissues.

Cordarone X is strongly protein-bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half-life of more than 100 days has been reported. High doses of Cordarone X, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the drug, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

Inactive ingredients include: Cordarone X 200 and Cordarone X 100 Tablets – lactose; Cordarone X Intravenous – Benzyl alcohol and polysorbate 80.

Product licence numbers

Cordarone X 100	0623/0017
Cordarone X 200	0623/0007
Cordarone X Intravenous	0623/0012

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing Cosbiol (Squalane) 3.0%, hexachlorophane 0.5%, allantoin 0.2%.

Uses Prevention of pressure sores. Prevention and treatment of incontinence rash and non-specific rashes. Skin antiseptic for preparation of split-skin donor areas. As a hand cream for medical and surgical staff to reduce the risk of cross infection.

Dosage and administration Apply sparingly as a routine procedure every 4 to 6 hours and after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Contra-indications, warnings, etc Dermalex skin lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex should not be administered except on medical advice to children under two years of age.

Pharmaceutical precautions No special storage requirements.

Legal category P.

Package quantities 100 mls (OP).
250 mls (Pump action dispenser with this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It maintains its deep antiseptic activity in the skin for at least six hours, and in addition Cosbiol provides a beneficial effect for patients with dry skin.

Product licence number 1983/5000.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate BP.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate BP.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate BP.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate BP per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate BP per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in

combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc
Contra-indication: Active liver disease.

Side-effects
Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been reported rarely.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and aspirin). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated.

There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place below 30°C.

Epilim Syrup and Epilim Liquid should be kept below 30°C and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate BP 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced if sedation is observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Active liver disease.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been reported occasionally and appear to be dose-related effects.

Sedation has been occasionally reported, usually in combination with other anticonvulsants. In Epilim monotherapy it occurs on rare occasions early in treatment and is usually transient. It is possible that rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations may occur.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g warfarin and aspirin). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated.

There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and drowsiness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be severe CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2–8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack of one vial of 400 mg Sodium Valproate BP and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 5% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8 –20 hours.

Product licence numbers

Vial of freeze dried powder	0623/0038
Ampoule of solvent	0623/0040

OSSOPAN®

Presentation The active ingredient of Ossopan preparations is microcrystalline hydroxyapatite compound (MCHC), which is a source of calcium and phosphorus in a protein base containing trace elements.

Ossopan 800 tablets: Pale buff, film-coated. Each tablet contains 830 mg MCHC, providing 178 mg calcium and 83 mg phosphorus.

Ossopan granules: Coarse, brown granules, with a taste and odour of malt and cocoa. Each sachet contains 3320 mg MCHC, providing 712 mg calcium and 332 mg phosphorus. Each sachet contains approximately 4 grams, equivalent to 4 Ossopan 800 tablets.

Uses Provision of calcium and phosphorus in osteoporosis, rickets, osteomalacia and during lactation.

Dosage and administration
Ossopan 800: 4–8 tablets to be taken daily in divided doses, before meals.

Ossopan granules: One to two sachets daily with or before food.

Use in the elderly: There are no special dosage recommendations.

Contra-indications, warnings, etc
Contra-indications: Hypercalcaemia, hypercalciuria.

Precautions: Care should be exercised in patients with severe immobilisation, e.g. paraplegia, and in patients with a history of renal calcium stone formation.

Treatment of overdosage: No cases of intoxication with Ossopan due to deliberate or accidental overdosage have been reported to the Company. It is considered that overdosage is unlikely to be a problem.

Pharmaceutical precautions Store in a dry place.

Legal category P.

Package quantities
Ossopan 800: packs of 50 tablets.
Ossopan granules: packs containing 28 sachets (OP).

Further information Hydroxyapatite is the complex biological calcium salt which forms the basis of skeletal structure; its overall formula is $Ca_{10}(PO_4)_6(OH)_2$. MCHC contains about 50 per cent hydroxyapatite and X-ray diffraction studies have confirmed the presence and microcrystalline nature of the salt. It also contains many essential trace elements together with natural skeletal protein (collagen), substituent amino acids and glycosaminoglycans. Clinical studies suggest that MCHC may be more readily assimilable than synthetic calcium supplements.

Product licence numbers

Ossopan 800 tablets	0378/0001
Ossopan granules	0623/0046

TRIFYBA®

Presentation Trifyba is a light brown particulate powder containing 80% of fibre, dervied from the husk of wheat (Testa Triticum Tricum). It is presented as single dose sachets each containing 3.5 g.

Uses Colonic and gastro-intestinal disorders where a high-fibre regimen is indicated including simple constipation, uncomplicated diverticular disease, irritable colon, haemorrhoidal disorders and fissures and other conditions where straining at stool should be avoided.

Dosage and administration
Adults: One sachet two to three times daily.

all subfractions, and a decrease in apolipoproteins AI and AII, is likely with Danol in the female. The clinical significance of these changes is not established.

Reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free thyroxin index, is also likely during therapy.

Haematuria has rarely been reported with prolonged use in patients with hereditary angioedema.

Overdosage: In animal tests, doses of 16,000 mg/kg body weight produced no fatalities and it is unlikely that any immediate serious reactions would be seen from a single excessive dose in man.

In the case of acute overdosage, the drug should be removed by emesis or stomach pump (if ingestion is recent) and the patient should be kept under observation in case of any delayed reactions.

Pharmaceutical precautions Nil.

Legal category POM.

Package quantities Danol 200 mg capsules are supplied in cartons of 100 in blisters and as Danol 200 C-Pak in calendar packs of 56 (OP).
Danol 100 mg capsules are supplied in cartons of 100 in blisters.

Further information Nil.

Product licence numbers
Danol 200 mg 0071/0095
Danol 100 mg 0071/0094

Product licence holder: Sterling-Winthrop Group Ltd.

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing hexachlorophane 0.5%, in an emollient base.

Uses For topical application as an antiseptic emollient in areas of unbroken skin where infection is likely; including the sacral area and pressure points in the immobile elderly.

Dosage and administration
Adults and children over 2 years: Apply sparingly as a routine procedure every 4 to 6 hours after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Children below 2 years: Not recommended except on the advice of a physician.

Use in the elderly: As for adults.

Contra-indications, warnings, etc Dermalex lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex lotion is contra-indicated in pregnancy and in nursing mothers.

Dermalex should not be administered except on medical advice to children under two years of age.

Use in pregnancy: There is evidence that hexachlorophane is a hazard to neonates. It is therefore advised that the product should not be used during pregnancy or by lactating mothers.

Treatment of overdose: No cases of intoxication with Dermalex due to deliberate or accidental ingestion have been reported to the Company. It is considered that overdosage from ingestion is unlikely to be a problem.

Pharmaceutical precautions Store at a temperature not exceeding 25°C.

Legal category P.

Package quantities 100 ml (OP).
250 ml (Pump action dispenser available for this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It has long-acting antiseptic activity on the skin.

Product licence number 1983/5000.

Product licence holder: The Dermalex Co. Ltd.

EPILIM®

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate BP.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate BP.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate BP.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate BP per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate BP per 5 ml.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction in dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely, gynaecomastia has occurred.

Drug interactions: Like many other drugs, Epilim may potentiate the effects of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim, and these should be monitored particularly the free form.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be

serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place below 30°C. Epilim Syrup and Epilim Liquid should be kept below 30°C and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Inactive ingredients include:
Epilim Enteric Coated – E123
Epilim Syrup – Sucrose, Ponceau 4R, Parabens
Epilim Liquid – Ponceau 4R, Parabens, Sorbitol

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

Product licence holder: Elf Sanofi UK Ltd.

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate BP 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicy-

lates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Other: Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment which may include assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C, infusion solutions at 2–8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack of one vial of 400 mg Sodium Valproate BP and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Product licence numbers

Vial of freeze dried powder	0623/0038
Ampoule of solvent	0623/0040

Product licence holder: Elf Sanofi UK Ltd.

ERADACIN®

Presentation Eradacin capsules are No. 1 opaque red/yellow capsules filled with a white powder. Each capsule contains 150 mg acrosoxacin (rosoxacin I.N.N.) Eradacin capsules contain lactose.

Uses Eradacin is for the treatment of acute gonorrhoea infection in both male and female patients.

Dosage and administration Eradacin is for oral administration only.

Adults including the elderly: A single dose of two capsules (300 mg) preferably on an empty stomach.

Children and growing adolescents: Not recommended.

Contra-indications, warnings, etc Safe use during human pregnancy has not yet been established and Eradacin should be used only when necessitated by the anticipated bacteriological and clinical benefits.

It should be used with caution in patients with impaired renal or hepatic function.

Because Eradacin may cause dizziness and drowsi-

ousness and changes in libido. Dizziness, vertigo, nausea, headache, fatigue and epigastric and pleuritic pain have also been noted.

A temporary alteration of lipoproteins in the form of an increase in LDL cholesterol, a decrease in HDL, affecting all subfractions, and a decrease in apolipoproteins AI and AII, is likely with Danol in the female. The clinical significance of these changes is not established.

Reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free thyroxin index, is also likely during therapy.

Haematuria has rarely been reported with prolonged use in patients with hereditary angioedema.

Overdosage: In animal tests, doses of 16,000 mg/kg body weight produced no fatalities and it is unlikely that any immediate serious reactions would be seen from a single excessive dose in man.

In the case of acute overdosage, the drug should be removed by emesis or stomach pump (if ingestion is recent) and the patient should be kept under observation in case of any delayed reactions.

Pharmaceutical precautions Nil.

Legal category POM.

Package quantities Danol 200 mg capsules are supplied in cartons of 100 in blisters and as Danol 200 C-Pak in calendar packs of 56 (OP).
Danol 100 mg capsules are supplied in cartons of 100 in blisters.

Further information Nil.

Product licence numbers
Danol 200 mg 11723/0016
Danol 100 mg 11723/0015

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing hexachlorophane 0.5%, in an emollient base.

Uses For topical application as an antiseptic emollient in areas of unbroken skin where infection is likely: including the sacral area and pressure points in the immobile elderly.

Dosage and administration
Adults and children over 2 years: Apply sparingly as a routine procedure every 4 to 6 hours after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Children below 2 years: Not recommended except on the advice of a physician.

Use in the elderly: As for adults.

Contra-indications, warnings, etc Dermalex lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex lotion is contra-indicated in pregnancy and in nursing mothers.

Dermalex should not be administered except on medical advice to children under two years of age.

Use in pregnancy: There is evidence that hexachlorophene is a hazard to neonates. It is therefore advised that the product should not be used during pregnancy or by lactating mothers.

Treatment of overdose: No cases of intoxication with Dermalex due to deliberate or accidental ingestion have been reported to the Company. It is considered that overdosage from ingestion is unlikely to be a problem.

Pharmaceutical precautions Store at a temperature not exceeding 25°C.

Legal category P.

Package quantities 100 ml (OP).
250 ml (Pump action dispenser available for this size)

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It has long-acting antiseptic activity on the skin.

Product licence number 1983/5000.
Product licence holder: The Dermalex Co. Ltd.

EPILIM® EPILIM CHRONO® CONTROLLED RELEASE

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate PhEur.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate PhEur.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate PhEur.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate PhEur per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate PhEur per 5 ml.

6. *Epilim Chrono 200:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 200 mg Sodium Valproate.

7. *Epilim Chrono 300:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 300 mg Sodium Valproate.

8. *Epilim Chrono 500:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 500 mg Sodium Valproate.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim and Epilim Chrono should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increased by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved, this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day, in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Epilim Chrono formulations are not suitable in this group of patients, due to the need for dose titration.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. The

affect the clinical interpretation of plasma valproic acid levels.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Epilim Chrono is a controlled release formulation of valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day. Epilim Chrono is to be given twice daily. The tablets must be swallowed whole and not crushed.

Combined therapy. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim or Epilim Chrono. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be useful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Severe or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim or Epilim Chrono should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In monotherapy it has occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim or Epilim Chrono with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely, gynaecomastia has occurred.

Drug interactions: Like many other drugs, Epilim may potentiate the effects of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by valproate, and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Valproate may inhibit the metabolism of lamotrigine.

Dosage of Epilim or Epilim Chrono may require adjustment when used in combination with other

anticonvulsants. See Dosage, Combined Therapy Section.

There is evidence that cimetidine, but not ranitidine, may prolong the half life and reduce clearance of valproate.

The absorption of valproate may be decreased in the presence of cholestyramine.

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receivinganti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim and Epilim Chrono tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place below 30°C. Epilim Syrup and Epilim Liquid should be kept below 30°C and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets, Epilim 100 mg Crushable tablets and Epilim Chrono tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim and Epilim Chrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Epilim Chrono formulations are controlled release formulations which demonstrate in pharmacokinetics studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

Inactive ingredients in accordance with ABPI Guidelines are:
Epilim Enteric Coated – E123.
Epilim 100 mg Crushable – None.
Epilim Syrup – Sucrose, Ponceau 4R, Parabens.
Epilim Liquid – Ponceau 4R, Parabens, Sorbitol.

Product licence numbers

Epilim Syrup	11723/0025
Epilim 500 Enteric-Coated	11723/0023
Epilim 200 Enteric-Coated	11723/0016
Epilim 100 mg Crushable tablets	11723/0017
Epilim Liquid	11723/0024
Epilim Chrono 200	11723/0078
Epilim Chrono 300	11723/0021
Epilim Chrono 500	11723/0079

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile freeze dried Sodium Valproate PhEur 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections PhEur).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20-30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day, but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Continual therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Other: Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Epilim may inhibit the metabolism of lamotrigine.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

There is evidence that cimetidine, but not ranitidine, may prolong the half-life and reduce clearance of Epilim.

The absorption of Epilim may be decreased in the presence of cholestyramine.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment which may include assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2–8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack containing one vial of 400 mg Sodium Valproate PhEur and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Product licence numbers

Vial of freeze dried powder	11723/0022
Ampoule of solvent	11723/0023

ERADACIN®

Presentation Eradacin capsules are No. 1 opaque, red/yellow capsules filled with a white powder. Each capsule contains 150 mg pefloxacin (pefloxacin [A.N.])

Adults including the elderly: A single dose of two capsules (300 mg) preferably on an empty stomach.

Children and growing adolescents: Not recommended.

Contra-indications, warnings, etc Safe use during human pregnancy has not yet been established and Eradacin should be used only when necessitated by the anticipated bacteriological and clinical benefits.

It should be used with caution in patients with impaired renal or hepatic function.

Because Eradacin may cause dizziness and drowsiness, patients should be warned not to drive or operate machinery if affected.

Eradacin has been shown to induce lesions in weight-bearing joints of young animals receiving high, single or repeated doses. The relevance of this to man is unknown but it is recommended that frequent, repeated doses should not be given to those under 18 years of age.

It is recognised that convulsions may occur due to an interaction between quinolones and non-steroidal anti-inflammatory drugs. This has not however been observed so far with rosoxacin.

Side-effects: Occasionally headaches, gastro-intestinal upsets, dizziness and drowsiness may occur.

Overdosage: Animal toxicity studies suggest that CNS depression is a likely symptom of overdosage. If vomiting does not occur, the drug should be removed by emesis or gastric lavage, if ingestion is recent, and symptomatic treatment applied.

Pharmaceutical precautions None.

Legal category POM.

Package quantities Eradacin is supplied in blister packs of 20 capsules.

Further information A single dose of 300 mg Eradacin has been shown to produce a cure rate of over 90% in cases of uncomplicated gonococcal urethritis. Treatment with Eradacin may be successful in patients infected with *N. gonorrhoeae* strains resistant to penicillin and other antibiotics.

Product licence number 11723/0026.

FERGON®

Presentation Fergon Tablets are smoothly polished red, sugar-coated tablets with no markings, each containing 300 mg Ferrous Gluconate PhEur, which provides 35 mg elemental iron. Fergon Tablets contain dextrose, sucrose, Cannoisine (E122) and Ponceau 4R(E124).

Uses Fergon Tablets are recommended for the treatment and prophylaxis of uncomplicated iron deficiency anaemia.

Dosage and administration Fergon is for oral administration. It is best administered about one hour before meals.

Adults (including the elderly and pregnant women after the second trimester):

Prophylactic: 2 tablets (600 mg) daily.

Therapeutic: 4–6 tablets (1.2–1.8 g) daily in divided doses.

Children: Children aged 6–12 years may be given 1–3 tablets daily for therapeutic purposes. A smaller dose may be sufficient for prophylaxis. Not recommended for children under 6 years.

Contra-indications, warnings, etc

Contra-indications: Fergon tablets should not be given to patients receiving repeated blood transfusions or those with haemosiderosis, haemochromatosis, haemolytic anaemia, active peptic ulcer, regional enteritis, ulcerative colitis or hypersensitivity to ferrous gluconate.

Precautions: Fergon should be used with caution in

Treatment of overdose: No cases of intoxication with Dermalex due to deliberate or accidental ingestion have been reported to the Company. It is considered that overdosage from ingestion is unlikely to be a problem.

Pharmaceutical precautions Store at a temperature not exceeding 25°C.

Legal category P.

Package quantities 100 ml (OP).
250 ml (Pump action dispenser available for this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It has long-acting antiseptic activity on the skin.

Product licence number 1983/5000.

Product licence holder: The Dermalex Co. Ltd.

EPILIM®
EPILIM CHRONO® CONTROLLED RELEASE

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate PhEur.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate PhEur.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate PhEur.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate PhEur per 5 ml.

5. *Epilim Liquid:* A red, cherry-flavoured, sugar-free liquid containing 200 mg Sodium Valproate PhEur per 5 ml.

6. *Epilim Chrono 200:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 200 mg Sodium Valproate.

7. *Epilim Chrono 300:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 300 mg Sodium Valproate.

8. *Epilim Chrono 500:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 500 mg Sodium Valproate.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim and Epilim Chrono should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2600 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Epilim Chrono formulations are not suitable in this group of patients, due to the need for dose titration.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Epilim Chrono is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day. Epilim Chrono is to be given twice daily. The tablets must be swallowed whole and not crushed.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim or Epilim Chrono. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at

risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim or Epilim Chrono should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In monotherapy it has occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim or Epilim Chrono with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely, gynaecomastia has occurred.

Drug interactions: Like many other drugs, Epilim may potentiate the effects of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by valproate, and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Valproate may inhibit the metabolism of lamotrigine.

Dosage of Epilim or Epilim Chrono may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

There is evidence that cimetidine, but not ranitidine, may prolong the half life and reduce clearance of valproate.

The absorption of valproate may be decreased in the presence of cholestyramine.

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim and Epilim Chrono tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place below 30°C. Epilim Syrup and Epilim Liquid should be kept below 30°C and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets, Epilim 100 mg Crushable tablets and Epilim Chrono tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim and Epilim Chrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Epilim Chrono formulations are controlled release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

Inactive ingredients in accordance with ABPI Guidelines are:
Epilim Enteric Coated – E123.
Epilim 100 mg Crushable – None.
Epilim Syrup – Sucrose, Ponceau 4R, Parabens.
Epilim Liquid – Ponceau 4R, Parabens, Sorbitol.

Product licence numbers

Epilim Syrup	11723/0025
Epilim 500 Enteric-Coated	11723/0020
Epilim 200 Enteric-Coated	11723/0018
Epilim 100 mg Crushable tablets	11723/0017
Epilim Liquid	11723/0024
Epilim Chrono 200	11723/0078
Epilim Chrono 300	11723/0021
Epilim Chrono 500	11723/0079

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate PhEur 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections PhEur).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see further information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy,

oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Other: Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Epilim may inhibit the metabolism of lamotrigine.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

There is evidence that cimetidine, but not ranitidine, may prolong the half-life and reduce clearance of Epilim.

The absorption of Epilim may be decreased in the presence of cholestyramine.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment which may include assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2-8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack containing one vial of 400 mg Sodium

Valproate PhEur and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Product licence numbers

Vial of freeze dried powder	11723/0022
Ampoule of solvent	11723/0023

ERADACIN®

Presentation Eradacin capsules are No. 1 opaque, red/yellow capsules filled with a white powder. Each capsule contains 150 mg acrosoxacin (rosoxacin I.N.N.) Eradacin capsules contain lactose.

Uses Eradacin is for the treatment of acute gonorrhoea infection in both male and female patients.

Dosage and administration Eradacin is for oral administration only.

Adults including the elderly: A single dose of two capsules (300 mg) preferably on an empty stomach.

Children and growing adolescents: Not recommended.

Contra-indications, warnings, etc Safe use during human pregnancy has not yet been established and Eradacin should be used only when necessitated by the anticipated bacteriological and clinical benefits.

It should be used with caution in patients with impaired renal or hepatic function.

Because Eradacin may cause dizziness and drowsiness, patients should be warned not to drive or operate machinery if affected.

Eradacin has been shown to induce lesions in weight-bearing joints of young animals receiving high, single or repeated doses. The relevance of this to man is unknown but it is recommended that frequent, repeated doses should not be given to those under 18 years of age.

It is recognised that convulsions may occur due to an interaction between quinolones and non-steroidal anti-inflammatory drugs. This has not however been observed so far with rosoxacin.

Side-effects: Occasionally headaches, gastro-intestinal upsets, dizziness and drowsiness may occur.

Overdosage: Animal toxicity studies suggest that CNS depression is a likely symptom of overdosage. If vomiting does not occur, the drug should be removed by emesis or gastric lavage, if ingestion is recent, and symptomatic treatment applied.

Pharmaceutical precautions None.

Legal category POM.

Package quantities Eradacin is supplied in blister packs of 20 capsules.

Further information A single dose of 300 mg Eradacin has been shown to produce a cure rate of over 80% in cases of uncomplicated gonococcal urethritis. Treatment with Eradacin may be successful in patients infected with *N. gonorrhoeae* strains resistant to penicillin and other antibiotics.

Product licence number 11723/0026.

FORTAGESIC®

Presentation White tablets with bevelled edges 12.7 mm diameter, marked FORTAGESIC on one side. Each tablet provides Pentazocine BP 15 mg (as the hydrochloride) and Paracetamol PhEur 500 mg. Fortagesic tablets contain sodium metabisulphite.

Uses Fortagesic is a compound analgesic for the relief of moderate pain associated with musculo-skeletal disorders or injuries, such as bursitis, sprains, strains, fibrositis, sciatica and osteoarthritis, and for rheumatoid arthritis in patients sensitive to aspirin.

Dosage and administration Fortagesic is for oral administration only.

Adults including the elderly: 2 tablets up to four times daily.

Children: 7–12 years: 1 tablet every three to four hours. Not more than 4 doses to be taken in any 24 hour period. Not recommended for children under 7 years of age.

Contra-indications, warnings, etc

Contra-indications: Fortagesic should not be administered to patients with established respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and is also contraindicated in the presence of acute alcoholism, head injuries, conditions in which intracranial pressure is raised, acute bronchial asthma, in heart failure, secondary to chronic lung disease and in patients known to be hypersensitive to pentazocine or paracetamol.

Warnings:

Use in pregnancy and lactation: There is epidemiological evidence for the safety of paracetamol in human pregnancy. No such evidence exists for pentazocine but it has been widely used for many years without apparent ill consequences. In rodents, harmful effects in the foetus have been observed but only at doses high enough to cause maternal toxicity. Pentazocine can enter the foetal circulation and has the potential to cause opioid effects including central depression and abstinence syndrome in the foetus (see below). It does not appear to have significant adverse effects on uterine function at parturition. Nonetheless, careful consideration should be given to the use of Fortagesic during pregnancy, particularly during the first trimester, or at term.

There are insufficient data on the secretion of pentazocine in breast milk so it is recommended that infants of nursing mothers who are receiving high doses of Fortagesic be appropriately monitored.

Precautions:

Particular caution should be observed in administering Fortagesic to patients with porphyria, since it may provoke an acute attack in susceptible individuals, as well as in its use in patients who are receiving monoamine oxidase inhibitors or who have received them within the preceding 14 days.

Pentazocine can both depress as well as elevate blood pressure possibly through the release of endogenous catecholamines. Particular caution should be observed therefore in using Fortagesic in the presence of phaeochromocytoma, in the acute phase following myocardial infarction when it may increase pulmonary and systemic blood pressure and vascular resistance and in other clinical situations where alteration of vascular resistance or blood pressure might be particularly undesirable.

Caution should be observed in patients with renal or hepatic impairment and in elderly patients, who may additionally be especially sensitive to the effects of opioids, as both conditions may lead to an increase in bioavailability of pentazocine and call for a reduction in dosage.

Caution should also be observed in patients who are prone to seizures and in the presence of other opioids or opioid-dependence since the weak opioid

Warnings:
Use in pregnancy: There is epidemiological and toxicological evidence of hazard in human pregnancy. Danazol is known to be associated with the risk of virilisation to the female foetus if administered during human pregnancy. Danazol should not be used during pregnancy. Women of child bearing age should be advised to use an effective, non-hormonal method of contraception.

Use during lactation: Danazol has the theoretical potential for androgenic effects in breast-fed infants and therefore either danazol therapy or breast feeding should be discontinued.

Particular care should be observed when using Danol in patients with hepatic or renal disease, hypertension or other cardiovascular disease and in any state which may be exacerbated by fluid retention as well as in diabetes mellitus, polycythaemia, epilepsy, lipoprotein disorder, in those with a history of thrombosis and in those who have shown marked or persistent androgenic reaction to previous gonadal steroid therapy. Adjustment in concomitant therapy may be called for particularly in patients with hypertension, diabetes mellitus or epilepsy, when introducing or discontinuing Danol as well as during Danol treatment.

Caution is advised in patients with migraine. Until more is known, caution is also advised in the use of Danol in the presence of known or suspected malignant disease (see also Contra-indications). The presence of carcinoma should be excluded before continuing Danol therapy if breast nodules persist or enlarge during treatment.

In the event of virilisation, Danol should be withdrawn. Whilst androgenic reactions will generally prove reversible, continued use of Danol in the face of evident virilisation is likely to cause irreversible change.

In addition to clinical monitoring in all patients, appropriate laboratory monitoring should be considered which may include periodic measurement of hepatic function and haematological state.

Experience of long term therapy with Danol is limited. Whilst a course of therapy may need to be repeated, care should be observed. The long term risk of 17-alkylated steroids (including benign hepatic adenomata and peliosis hepatis), should be considered when danazol, which is chemically related to these compounds is used for periods longer than those normally recommended.

Interactions: Anti-convulsant therapy: Danol may affect the plasma level of carbamazepine and, possibly, the patient's response to this agent and to phenytoin. With phenobarbitone it is likely that similar interaction would occur.

Anti-diabetic therapy: Danol can cause insulin resistance.

Anti-coagulant therapy: Danol can potentiate the action of warfarin.

Anti-hypertensive therapy: possibly through promotion of fluid retention, Danol can oppose the action of anti hypertensive agents.

Cyclosporin: Danol can increase the plasma level of cyclosporin.

Concomitant steroids: although specific instances have not been described, it is likely that interactions will occur between Danol and gonadal steroid therapy.

Migraine therapy: Danol may itself provoke migraine and possibly reduce the effectiveness of medication to prevent that condition.

Ethyl alcohol: subjective intolerance in the form of nausea and shortness of breath has been reported.

Alfacalcidol: Danol may increase the calcaemic response in primary hypoparathyroidism necessitating a reduction in dosage of this agent.

Side-effects: The possible causal relationship between Danol and many of the following events reportedly associated with its use remains to be defined.

Androgenic effects include weight gain, acne and seborrhoea. Hirsutism, hair loss, voice change, which may take the form of hoarseness, sore throat or of instability or deepening of pitch, may occur. Hypertrophy of the clitoris is rare.

Other possible endocrine effects include menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhoea. Although cyclical bleeding and ovulation usually return within 60-90 days after Danol, persistent amenorrhoea has occasionally been reported. Flushing, vaginal dryness and irritation and reduction in breast size, may reflect lowering of oestrogen. In the male a modest reduction in spermatogenesis may be evident during treatment.

Insulin resistance may be increased in diabetes mellitus, but symptomatic hypoglycaemia in non-diabetic patients has also been reported as has an increase in plasma glucagon level.

Danol may aggravate epilepsy and expose the condition in those so predisposed.

Cutaneous reactions include rashes, which may be maculopapular, petechial, or purpuric or may take an urticarial form and may be accompanied by facial oedema. Associated fever has also been reported. Rarely, sun-sensitive rash has been noted. Inflammatory erythematous nodules, changes in skin pigmentation and exfoliative dermatitis have also been reported.

Musculo-skeletal reactions include backache and muscle cramps which can be severe. Creatine phosphokinase levels may also rise. Muscle tremors, fasciculation, limb pain, joint pain and joint swelling have also been reported.

Cardiovascular reactions may include exacerbation of hypertension, palpitation and tachycardia.

Benign intracranial hypertension, visual disturbances which may take the form of blurring or difficulty in focusing and in wearing contact lenses or need for temporary alteration in refractive correction, have been noted.

Haematological responses include an increase in red cell and platelet count. Reversible erythrocytosis or polycythaemia may be provoked. Eosinophilia, leucopenia and thrombocytopenia have also been noted.

Arterial or venous thrombosis is unlikely because danazol activates both the fibrinolytic system and inhibitors in the clotting cascade. Clinical and epidemiological evidence supports this conclusion. Rare occurrences of sagittal sinus and cerebrovascular thrombosis have been observed but their association with danazol is unclear.

Hepatic reactions include modest increases in serum transaminase levels, and, rarely, cholestatic jaundice. Benign hepatic adenomata and peliosis hepatis have been observed with long term use.

Fluid retention may explain the occasional reports of carpal tunnel syndrome. Danol may also provoke migraine.

Possible psychical reactions include increased appetite, emotional lability, anxiety, depressed mood, nervousness and changes in libido. Dizziness, vertigo, nausea, headache, fatigue and epigastric and pleuritic pain have also been noted.

A temporary alteration of lipoproteins in the form of an increase in LDL cholesterol, a decrease in HDL, affecting all subfractions, and a decrease in apolipoproteins AI and AII, is likely with Danol in the female. The clinical significance of these changes is not established.

Reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free thyroxin index, is also likely during therapy.

Haematuria has rarely been reported with prolonged use in patients with hereditary angioedema.

Overdosage: In animal tests, doses of 16,000 mg/kg body weight produced no fatalities and it is unlikely that any immediate serious reactions would be seen from a single excessive dose in man.

In the case of acute overdosage, the drug should be removed by emesis or stomach pump (if ingestion is recent) and the patient should be kept under observation in case of any delayed reactions.

Pharmaceutical precautions Nil.

Legal category POM.

Package quantities Danol 200 mg capsules are supplied in cartons of 100 in blisters and as Danol 200 C-Pak in calendar packs of 50 (OP).
Danol 100 mg capsules are supplied in cartons of 100 in blisters.

Further information Nil.

Product licence numbers

Danol 200 mg	11723/0016
Danol 100 mg	11723/0015

DERMALEX® SKIN LOTION

Presentation A white oil-in-water emulsion containing hexachlorophane 0.5%, in an emollient base.

Uses For topical application as an antiseptic emollient in areas of unbroken skin where infection is likely; including the sacral area and pressure points in the immobile elderly.

Dosage and administration
Adults and children over 2 years: Apply sparingly as a routine procedure every 4 to 6 hours after washing.

Only a thin film is needed on the skin for good results. Over generous application can occasionally cause redness.

It is important to ensure that no barrier creams are used on a patient using Dermalex skin lotion.

Children below 2 years: Not recommended except on the advice of a physician.

Use in the elderly: As for adults.

Contra-indications, warnings, etc Dermalex lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes. During regular use in the treatment of pressure areas it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Dermalex lotion is contra indicated in pregnancy and in nursing mothers.

Dermalex should not be administered except on medical advice to children under two years of age.

Use in pregnancy: There is evidence that hexachlorophane is a hazard to neonates. It is therefore advised that the product should not be used during pregnancy or by lactating mothers.

Treatment of overdose: No cases of intoxication with Dermalex due to deliberate or accidental ingestion have been reported to the Company. It is considered that overdosage from ingestion is unlikely to be a problem.

Pharmaceutical precautions Store at a temperature not exceeding 25°C.

Legal category P.

Package quantities 100 ml (OP).
250 ml (Pump action dispenser available for this size).

Further information Dermalex is a deep penetrating lotion effective against a wide range of organisms and with a long allergy free history. It has long acting antiseptic activity on the skin.

Product licence number 1983/5000.

Product licence holder: The Dermalex Co. Ltd.

1986 -87

EPILIM®
EPILIM CHRONO® CONTROLLED RELEASE

Presentation

1. *Epilim 200 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 200 mg Sodium Valproate PhEur.

2. *Epilim 500 Enteric-Coated:* A lilac-coloured enteric-coated tablet containing 500 mg Sodium Valproate PhEur.

3. *Epilim 100 mg Crushable Tablets:* A white scored tablet containing 100 mg Sodium Valproate PhEur.

4. *Epilim Syrup:* A red, cherry-flavoured syrup containing 200 mg Sodium Valproate PhEur per 5 ml.

5. *Epilim Liquid:* A red, cherry flavoured, sugar-free liquid containing 200 mg Sodium Valproate PhEur per 5 ml.

6. *Epilim Chrono 200:* A lilac coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 200 mg Sodium Valproate.

7. *Epilim Chrono 300:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 300 mg Sodium Valproate.

8. *Epilim Chrono 500:* A lilac-coloured, controlled release tablet containing a mixture of Sodium Valproate PhEur and Valproic Acid FrP equivalent to 500 mg Sodium Valproate.

Uses In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim and Epilim Chrono should be used only in severe cases or in those resistant to other treatment.

Dosage and administration Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Epilim Chrono formulations are not suitable in this group of patients, due to the need for dose titration.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Epilim

in patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Administration: Epilim Tablets, Syrup and Liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Epilim Chrono is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day. Epilim Chrono may be given once or twice daily. The tablets must be swallowed whole and not crushed.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim or Epilim Chrono. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim or Epilim Chrono should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In monotherapy it has occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim or Epilim Chrono with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely, gynaecomastia has occurred.

Drug interactions: Like many other drugs, Epilim may potentiate the effects of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Aspirin may displace valproate from binding sites resulting in higher free levels of valproate. Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by valproate, and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Valproate may inhibit the metabolism of lamotrigine.

Dosage of Epilim or Epilim Chrono may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

There is evidence that cimetidine, but not ranitidine, may prolong the half life and reduce clearance of valproate.

The absorption of valproate may be decreased in the presence of cholestyramine.

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 6 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim and Epilim Chrono tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place below 30°C. Epilim Syrup and Epilim Liquid should be kept below 30°C and away from direct sunlight.

Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric Coated, Epilim 500 Enteric-Coated tablets, Epilim 100 mg Crushable tablets and Epilim Chrono tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim and Epilim Chrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Epilim Chrono formulations are controlled release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

Inactive ingredients in accordance with ABPI Guidelines are:

Epilim Enteric Coated – E123.
Epilim 100 mg Crushable – None.
Epilim Syrup – Sucrose, Ponceau 4R, Parabens.
Epilim Liquid – Ponceau 4R, Parabens, Sorbitol.

Product licence numbers

Epilim Syrup	11723/0025
Epilim 500 Enteric-Coated	11723/0020
Epilim 200 Enteric-Coated	11723/0018
Epilim 100 mg Crushable tablets	11723/0017
Epilim Liquid	11723/0024
Epilim Chrono 200	11723/0078
Epilim Chrono 300	11723/0021
Epilim Chrono 500	11723/0079

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate PhEur 400 mg in a

clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections PhEur).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 85 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Other: Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Epilim may inhibit the metabolism of lamotrigine.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

There is evidence that cimetidine, but not ranitidine, may prolong the half-life and reduce clearance of Epilim.

The absorption of Epilim may be decreased in the presence of cholestyramine.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment which may include assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2–8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack containing one vial of 400 mg Sodium Valproate PhEur and one ampoule containing 4 ml of solvent.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8–20 hours.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free serum valproic acid levels.

Product licence numbers

Vial of freeze dried powder	11723/0022
Ampoule of solvent	11723/0023

ERADACIN® CAPSULES

Qualitative and quantitative composition Rosoxacin 150 mg.

Pharmaceutical form Capsule.

Clinical particulars

Therapeutic indications: Eradacin is for the treatment of acute gonorrhoea infection in both male and female patients.

Posology and method of administration: Adults including the elderly: Two capsules (300 mg) preferably on an empty stomach.

Children and growing adolescents: Eradacin capsule are not recommended for children or growing adolescents.

Eradacin capsules are for oral administration only.

Contra indications: None stated.

Special warnings and special precautions for use: Eradacin should be used with caution in patients with impaired renal or hepatic function. Eradacin has been shown to induce lesions in weight bearing joints of young animals receiving high, single or repeated doses. The relevance of this to man is unknown but it is recommended that frequent repeated doses should not be given to those under 18 years of age.

Interaction with other medicaments and other forms of interaction: It is recognised that convulsions may occur due to an interaction between quinolones and non steroidal anti-inflammatory drugs. This has not however been observed so far with rosoxacin.

Pregnancy and lactation: Safe use during pregnancy has not yet been established and Eradacin should be

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oestradiol in plasma is about one hour. Oestradiol is metabolised mainly in the liver. The most important metabolites are oestriol, oestrone and their conjugates (glucuronides, sulphates), which are much less active than oestradiol. The metabolites of oestradiol are eliminated mainly by the kidney as glucuronides and sulphates.

The majority of orally-administered oestradiol is metabolised to oestrone and its conjugates by the intestine and the liver before reaching the circulation, giving rise to high, unphysiological levels of oestrone in the blood. The consequences of chronic accumulation of oestrone in the body are not yet clear. However, it has been confirmed that prolonged oral administration of oestrogens leads to increased protein synthesis by the liver, in particular of renin substrate, resulting in hypertension.

Following cutaneous application of Dermestril, oestradiol is released from the drug-containing adhesive matrix through the skin and reaches the systemic circulation directly, avoiding first-pass metabolism by the liver, and hence avoiding hepatic protein synthesis stimulation and oestrone accumulation. Consequently, the oestradiol: oestrone ratio in plasma, which falls to values below 1 after the menopause and during oral oestrogen replacement therapy, returns to premenopausal levels (approximately 1) with transdermal oestradiol. The nominal daily in vivo release rates of Dermestril 25, 50 and 100 are 25 mcg, 50 mcg, and 100 mcg of oestradiol, respectively; the system is active for four days. These release rates result in physiological oestradiol serum concentrations, i.e. those of the premenopausal early follicular phase, which are constantly maintained throughout the patch application period.

After a single application of Dermestril with a daily oestradiol release of 100 mcg in postmenopausal women, physiological serum levels of oestradiol were reached approximately four hours after application and mean maximum serum oestradiol levels of 70 pg/mL were obtained. The serum concentration of oestradiol remained within the physiological levels of premenopausal women throughout the 3-4 days of the application period and returned to baseline within 12 hours after removal of Dermestril.

Following repeated applications of Dermestril 50 patches at 84-96 hour intervals, steady-state was reached during application of the second patch and no accumulation was observed thereafter.

Preclinical safety data: As oestradiol is a physiological hormone, which has been used for many years in clinical therapy in a variety of pharmaceutical forms and which is very well documented in the scientific literature, only local tolerance to Dermestril has been examined. Local tolerance studies performed in the rabbit after single and repeated applications of Dermestril showed good skin tolerability of the system. A skin sensitisation test performed in the guinea pig did not show any sensitising potential of Dermestril.

Primary skin irritation tests and sensitisation tests performed on the acrylic copolymers that form the adhesive matrix demonstrated the topical safety of these components.

Pharmaceutical particulars

List of excipients: Oestradiol-containing adhesive matrix: acrylic copolymers. Backing foil: polyethylene terephthalate. Each transdermal delivery system is covered by a protective liner (siliconised polyethylene terephthalate) which is removed prior to use.

Incompatibilities: No pharmaceutical incompatibilities are known.

Shelf life: Two years in the intact sachets, when stored as recommended.

Special precautions for storage: Dermestril should be stored below 25°C.

Nature and contents of container: Carton of 8 transdermal delivery systems, each sealed individually in protective sachets of heat-sealable material with an internal aluminium layer.

Instructions for use/handling: Tear open the sachet at the indentation (do not use scissors to avoid damaging the patch) and remove the patch. Hold the patch between the thumb and index finger at the corner with the pull-off tag. Detach the protective liner with the other hand and discard it.

Do not touch the adhesive side of the patch. Apply the patch to the skin holding between the thumb and index finger the part still covered by the protective liner. Detach the remaining part of the protective liner and press firmly for about 10 seconds on the whole surface of the patch. Pass a finger along the edges to assure good adhesion.

Marketing authorisation numbers
Dermestril 25 11723/0218
Dermestril 50 11723/0219
Dermestril 100 11723/0220

Date of approval/revision of SPC April 1997.

Legal category POM.

EPILIM®

Qualitative and quantitative composition

Epilim 500 Enteric Coated: 500 mg Sodium Valproate PhEur.

Epilim 200 Enteric Coated: 200 mg Sodium Valproate PhEur.

Epilim 100 mg Crushable: 100 mg Sodium Valproate PhEur.

Epilim Syrup and Liquid: 200 mg Sodium Valproate PhEur per 5 ml.

Pharmaceutical form

Epilim 500 Enteric Coated: Enteric coated tablets.
Epilim 200 Enteric Coated: Enteric coated tablets.
Epilim 100 mg Crushable: Tablets.
Epilim Syrup: Syrup.
Epilim Liquid: Liquid.

Clinical particulars

Therapeutic indications: In the treatment of generalised, partial or other epilepsy. In women of child bearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Posology and method of administration: Epilim tablets, syrup and liquid are for oral administration. Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug related, porphyria.

Special warnings and special precautions for use:

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

If it is necessary to dilute Epilim Syrup, the recommended diluent is syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life.

Interactions with other medicaments and other forms of interaction: Like many other drugs, Epilim may potentiate the effects of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem. Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Aspirin may displace valproate from binding sites resulting in higher free levels of valproate. Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects.

Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form, which may increase following an initial decrease in total levels.

Valproate may inhibit the metabolism of lamotrigine, dosages should be adjusted if lamotrigine dosage decreased) when appropriate.

Dosage of Epilim may require adjustments when used in combination with other anticonvulsants. See *Dosage, Combined Therapy* section.

There is evidence that cimetidine, (but not ranitidine) and erythromycin may prolong the half life and reduce clearance of valproate, and also that mefloquine may decrease serum levels of valproate.

The absorption of valproate may be decreased in the presence of cholestyramine.

Pregnancy and lactation: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contraindication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Effects on ability to drive and to use machines: Not applicable. Use of Epilim may provide seizure control such that the patient may again be eligible to hold a driving licence.

Undesirable effects:

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage. Patients with such

biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been rarely reported. When an abnormality of the urea cycle is suspected (ornithine transcarbamylase deficiency), pre-treatment ammonia levels should be measured.

Pancreatic: There have been reports of pancreatitis including, rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and frequent occurrence of thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests, that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur frequently in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has often been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported. Rarely signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus. The occurrence of vasculitis has occasionally been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness. In massive overdose, i.e., with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation and other supportive measures.

Pharmacological properties

Pharmacodynamic properties: Sodium valproate is an anticonvulsant. The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Pharmacokinetic properties: The half life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological or therapeutic effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Pre-clinical safety data: There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

Pharmaceutical particulars

List of excipients:

Enteric coated tablets: Polyvidone, talc, calcium silicate, magnesium stearate, hypromellose, citric acid anhydrous, polyethylene glycol, violet lake, methylated spirit, purified water, polyvinylacetate phthalate, diethyl phthalate and stearic acid.

Crushable tablets: Maize starch, kaolin light (naturall), silica hydrated, magnesium stearate and purified water).

Epilim Syrup: Sorbitol powder, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, sodium saccharin, sucrose, flavour IFF cherry 740, Ponceau 4R (E124) and purified water.

Epilim Liquid: Hydroxyethyl cellulose, sorbitol powder, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, saccharin sodium, Ponceau 4R (E124), flavour IFF cherry 740, citric acid anhydrous and purified water.
(1 not detected in final formulation.)

Incompatibilities: None.

Shelf life: Epilim Tablets and Syrup: 36 months. Epilim Liquid: 24 months.

Special precautions for storage:
Epilim Tablets: Store in a dry place below 30°C.
Epilim Syrup: Store below 30°C.
Epilim Liquid: Store below 30°C and away from direct sunlight. Epilim Liquid should not be diluted.

Nature and contents of container: Epilim Enteric Coated tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes of 100 and 112 tablets.

Epilim 100 mg Crushable Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes of 100 and 112 tablets.

Epilim Syrup and Liquid is supplied in amber glass bottles with polypropylene J-cap and amber polyethylene terephthalate bottles with polypropylene tamper evident closure. Bottle size 200 and 300 ml.

Instructions for use/handling: None.

Marketing authorisation numbers
Epilim 500 Enteric Coated 11723/0020.
Epilim 200 Enteric Coated 11723/0018.
Epilim Crushable 11723/0017.
Epilim Syrup 11723/0025.
Epilim Liquid 11723/0024.

Date of approval/revision of SPC April 1995.

Legal category POM.

EPILIM CHRONO*

Qualitative and quantitative composition

Epilim Chrono 200 Controlled Release tablets contain 133.2 mg Sodium Valproate PhEur and 58.0 mg Valproic Acid FP equivalent to 200 mg sodium valproate/tablet.

Epilim Chrono 300 Controlled Release tablets contain 199.8 mg Sodium Valproate PhEur and 87.0 mg Valproic Acid FP equivalent to 300 mg sodium valproate/tablet.

Epilim Chrono 500 Controlled Release tablets contain 333 mg Sodium Valproate PhEur and 145 mg Valproic Acid FP equivalent to 500 mg sodium valproate/tablet.

Pharmaceutical form Controlled release tablets.

Clinical particulars

Therapeutic indications: In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Posology and method of administration: Epilim Chrono Controlled Release tablets are for oral administration.

Epilim Chrono is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Epilim Chrono may be given once or twice daily. The tablets should be swallowed whole and not crushed.

Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: An alternative formulation of Epilim should be used in this group of patients, due to the need for dose titration.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Combined therapy: When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug related, porphyria.

Special warnings and special precautions for use:
Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Interactions with other medicaments and other forms of interaction: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g., warfarin and salicylates). Aspirin may displace valproate from binding sites resulting in higher free levels of valproate. Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects.

Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form, which may increase following an initial decrease in total levels. Valproate may inhibit the metabolism of lamotrigine, dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See *Dosage, Combined Therapy* section.

There is evidence that cimetidine, but not ranitidine, and erythromycin may prolong the half-life and reduce clearance of valproate, and also that mefloquine may decrease serum levels of valproate.

The absorption of valproate may be decreased in the presence of cholestyramine.

Pregnancy and lactation: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1–2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Effects on ability to drive and to use machines: Not applicable. Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Undesirable effects: Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children, particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigation in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis, e.g. prothrombin time, may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months, especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage.

Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time, should be monitored until they return to normal. However an abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been rarely reported. When an abnormality of the urea cycle is suspected (Ornithine transcarbamylase deficiency), pre-treatment ammonia levels should be measured.

Pancreatic: There have been reports of pancreatitis including, rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylases estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and frequent occurrence of thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests, that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it has occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion, occasionally progressing to stupor, somnilmes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur frequently in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss often has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus. The occurrence of vasculitus has occasionally been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Overdosage: Cases of accidental and suicidal valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentration 10 to 20 times maximum therapeutic levels, there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmacological properties

Pharmacodynamic properties: Sodium valproate is an anticonvulsant. The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Pharmacokinetic properties: The half life of sodium valproate is usually reported to lie within the range of 8–20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim Chrono may not be clearly correlated with the total of free (unbound) plasma valproic acid levels.

Epilim Chrono formulations are controlled release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

Pre-clinical safety data: There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical particulars

List of excipients: Hydroxypropylmethyl cellulose, ethylcellulose, hydrated silica.

Film coat: Violet coat, containing titanium dioxide (E171), erythrosine BS (E127), indigo carmine (E132), iron oxide black (E172), hydroxypropylmethyl cellulose (E464), polyethylene glycol 400, purified water†. († Not detected in final formulation.)

Incompatibilities: None.

Shelf life: Epilim Chrono tablets have a shelf life of 30 months.

Special precautions for storage: Store in a dry place below 30°C.

Nature and contents of container: Epilim Chrono Controlled Release tablets are supplied in blister packs further packed into a cardboard carton. Pack size 100 tablets.

Instructions for use/handling: Not applicable.

Marketing authorisation numbers

Epilim Chrono 200 Controlled Release 11723/0078
Epilim Chrono 300 Controlled Release 11723/0021
Epilim Chrono 500 Controlled Release 11723/0079

Date of approval/revision of SPC April 1996.

Legal category POM.

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate PhEur 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections PhEur).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 86 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 45 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: When starting Epilim in patients already on other anticonvulsants these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose reached after about 2 weeks. In certain cases it may be necessary to raise

the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturates should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see Further information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related. Porphyria.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine remeasurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely. When an abnormality of the urea cycle is suspected (ornithine transcarbamylase deficiency), pre-treatment ammonia levels should be measured.

Pancreatic: There have been reports of pancreatitis including rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, pancytopenia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment.

Dermatological: Transient hair loss has often been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Other: Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates). Aspirin may displace valproate from binding sites resulting in higher free levels of valproate. Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects. Phenytoin levels may be affected by Epilim and these should be monitored, particularly the free form which may increase following an initial decrease in total levels.

Epilim may inhibit the metabolism of lamotrigine. Dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

Dosage of Epilim may require adjustment when used in combination with other anti-convulsants. See 'Dosage, Combined Therapy Section'.

There is evidence that cimetidine (but not ranitidine) and erythromycin may prolong the half-life and reduce clearance of Epilim and also that mefloquine may decrease serum levels of valproate.

The absorption of Epilim may be decreased in the presence of cholestyramine.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1–2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Full recovery is usual following treatment which may include assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C; infusion solutions at 2-8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The Intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack containing one vial of 400 mg Sodium Valproate PhEur and one ampoule containing 4 ml of solvent.

Further information The half life of sodium valproate is usually reported to be within the range 8–20 hours, it is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micro mol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Product licence numbers

Vial of freeze dried powder	11723/0022
Ampoule of solvent	11723/0023

FORTAGESIC®

Presentation White tablets with bevelled edges 12.7 mm diameter, marked FORTAGESIC on one side. Each tablet provides Pentazocine BP 15 mg (as the hydrochloride) and Paracetamol PhEur 500 mg. Fortagesic tablets contain sodium metabisulphite.

Uses Fortagesic is a compound analgesic for the relief of moderate pain associated with musculoskeletal disorders or injuries, such as bursitis, sprains, strains, fibrositis, sciatica and osteoarthritis, and for rheumatoid arthritis in patients sensitive to aspirin.

Dosage and administration Fortagesic is for oral administration only.

Adults including the elderly: 2 tablets up to four times daily.

Children: 7–12 years: 1 tablet every three to four hours. Not more than 4 doses to be taken in any 24 hour period. Not recommended for children under 7 years of age.

Contra-indications, warnings, etc

Contra-indications: Fortagesic should not be administered to patients with established respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and is also contra-indicated in the presence of acute alcoholism, head injuries, conditions in which intracranial pressure is raised, acute bronchial asthma, in heart failure, secondary to chronic lung disease and in patients known to be hypersensitive to pentazocine or paracetamol.

Warnings:

Use in pregnancy and lactation: There is epidemiological evidence for the safety of paracetamol in human pregnancy. No such evidence exists for pentazocine but it has been widely used for many years without apparent ill consequences. In rodents, harmful effects in the foetus have been observed but only at doses high enough to cause maternal toxicity. Pentazocine can enter the foetal circulation and has the potential to cause opioid effects including central depression and abstinence syndrome in the foetus (see below). It does not appear to have significant adverse effects on uterine function at parturition. Nonetheless, careful consideration should be given to the use of Fortagesic during pregnancy, particularly during the first trimester, or at term.

dice. Rare occurrences of benign hepatic adenomata and peliosis hepatis have been observed with long term use.

Rare cases of pancreatitis have been reported.

Fluid retention may explain the occasional reports of carpal tunnel syndrome. Danol capsules may also provoke migraine.

Possible psychical reactions include increased appetite, emotional lability, anxiety, depressed mood, nervousness and changes in libido. Dizziness, vertigo, nausea, headache, fatigue and epigastric and pleuritic pain have also been noted.

A temporary alteration of lipoproteins in the form of an increase in LDL cholesterol, a decrease in HDL affecting all subfractions, and a decrease in apolipoproteins AI and AII have been reported with Danol in the female. The clinical significance of these changes is not established.

Other metabolic events have been reported, including induction of amino-levulinic acid (ALA) synthetase, and reduction in thyroid binding globulin, T4, with increased uptake of T3 but without disturbance of thyroid stimulating hormone or free thyroxine index, is also likely during therapy.

Haematuria has rarely been reported with prolonged use in patients with hereditary angioedema.

Overdose: Available evidence suggests that acute overdosage, would be unlikely to give rise to immediate serious reactions.

In the case of acute overdosage, the drug should be removed by emesis or stomach pump (if ingestion is recent) and the patient should be kept under observation in case of any delayed reactions.

Pharmacological properties

Pharmacodynamic properties: Danazol, 17α-pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol, is a synthetic steroid derived from ethisterone. Its pharmacological properties include:

1. Relatively marked affinity for androgen receptors, less marked affinity for progesterone receptors and least affinity for oestrogen receptors. Danazol is a weak androgen but in addition antiandrogenic, progestogenic, antiprogestogenic, oestrogenic and antioestrogenic actions have been observed.

2. Interference with the synthesis of gonadal steroids, possibly by inhibition of the enzymes of steroidogenesis, including 3β hydroxysteroid dehydrogenase, 17β hydroxysteroid dehydrogenase, 17 hydroxylase, 17,20 lyase, 11β hydroxylase, 21 hydroxylase and cholesterol side chain cleavage enzymes, or alternatively by inhibition of the cyclic AMP accumulation usually induced by gonadotrophic hormones in granulosa and luteal cells.

3. Inhibition of the mid-cycle surge of FSH and LH as well as alterations in the pulsatility of LH. Danazol can also reduce the mean plasma levels of these gonadotrophins after the menopause.

4. A wide range of actions on plasma proteins, including increasing prothrombin, plasminogen, antithrombin III, alpha 2 macroglobulin, C1 esterase inhibitor, and erythropoietin and reducing fibrinogen, thyroid binding and sex hormone binding globulins. Danazol increases the proportion and concentration of testosterone carried unbound in plasma. The suppressive effects of danazol on the hypothalamic-pituitary-gonadal axis are reversible, cyclical activity reappearing normally within 60–90 days after therapy.

Pharmacokinetic properties: Danazol is absorbed from the gastrointestinal tract, peak plasma concentrations of 60–90 ng/ml being reached approximately 2–3 hours after dosing. Compared to the fasting state, the bioavailability has been shown to increase 3 fold when the drug is taken with a meal with a high fat content. It is thought that food stimulates bile flow which facilitates the dissolution and absorption of danazol, a highly lipophilic compound.

The apparent plasma elimination half life of danazol in a single dose is approximately 3–6 hours. With multiple doses this may increase to approximately 26 hours.

None of the metabolites of danazol, which have been isolated, exhibits pituitary inhibiting activity comparable to that of danazol.

Few data on excretion routes and rates exist. In the monkey 36% of a radioactive dose was recoverable in the urine and 46% in the faeces within 96 hours.

Preclinical safety data: There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical particulars

List of excipients: Maize starch, lactose, purified talc, magnesium stearate.

Incompatibilities: None.

Shelf life: 60 months.

Special precautions for storage: None.

Nature and contents of container: PVC blister pack compound of polyvinyl chloride (thickness 250 μm) sealed to an aluminium foil (thickness 20 μm). The blister are then packed in a cardboard carton. Pack sizes: 50, 60 and 100 capsules.

Instructions for use/handling: Not applicable.

Marketing authorisation numbers
Danol 100 mg Capsules 11723/0015
Danol 200 mg Capsules 11723/0016

Date of approval/revision of SPC January 1998.

Legal category POM.

DERMALEX® SKIN LOTION

Qualitative and quantitative composition Dermalex Skin Lotion contains Hexachlorophane USP 0.5 w/v.

Pharmaceutical form Skin lotion.

Clinical particulars

Therapeutic indications: For topical application as an antiseptic emollient for use in areas of unbroken skin where infection is likely; including the sacral area and pressure points in the immobile elderly.

Posology and method of administration:
Adults and children over 2 years: Apply sparingly as a routine every 4 to 6 hours and after washing.

Dermalex should not be administered except on medical advice to children under 2 years of age.

Contra-indications: Dermalex Skin Lotion should not be applied to broken skin, open pressure sores, seriously burnt skin or mucous membranes.

Dermalex Skin Lotion is contra-indicated in pregnancy and in nursing mothers.

Dermalex should not be administered except on medical advice to children under two years of age.

Special warnings and special precautions for use: During regular use in the treatment of pressure sores it is inadvisable to apply to areas of the skin in excess of half of the total body surface area.

Interactions with other medicaments and other forms of interaction: It is important to ensure that no barrier creams are used on a patient using Dermalex Skin Lotion.

Pregnancy and lactation: There is evidence of hazard to neonates. It is therefore advised that the product should not be used during pregnancy or by lactating mothers.

Effects on ability to drive and to use machines: None known.

Undesirable effects: None known.

Overdose: No cases of intoxication with Dermalex Skin Lotion due to deliberate or accidental overdosage have been reported to the company. It is considered that overdosage is unlikely to be a problem.

Pharmacological properties

Pharmacodynamic properties: Hexachlorophane is a biophenol anti-bacterial agent which is particularly effective against gram positive organisms.

Pharmacokinetic properties: Hexachlorophane is absorbed onto the skin and multiple contact results in sustained degerming activity. It is absorbed through the skin but does not accumulate in the blood with continued use.

The majority of hexachlorophane is probably distributed very rapidly in the lipophilic tissue compartments. A small amount is slowly excreted unchanged in the urine.

The remainder is metabolised by the liver to glucoronide conjugate which is excreted in the bile and the faeces.

Preclinical safety data: There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical particulars

List of excipients: Squalane, allantoin, butylated hydroxyanisole, cetyl alcohol, decyloleate, lanoline anhydrous, octylstearate, propyl paraben, stearic acid, carbomer, triethanolamine, methyl paraben, disodium EDTA, sodium lauryl sulphate, sorbitol powder, perfume, water.

Incompatibilities: None known.

Shelf life: 36 months.

Special precautions for storage: To be stored at a temperature not exceeding 25°C.

Nature and contents of container: Blow moulded polyethylene bottle of 60 ml, 100 ml and 250 ml. 60 ml and 100 ml bottles have a polyethylene plug and polyethylene screw cap or a polypropylene screw cap and the 250 ml bottle has a polyethylene or polypropylene dispenser/cap.

Instructions for use/handling: Not applicable.

Marketing authorisation holder: The Dermalex Company Limited.

Marketing authorisation number 1983/5000R

Date of approval/revision of SPC October 1995.

Legal category P.

EPILIM®

Qualitative and quantitative composition
Epilim 500 Enteric Coated: 500 mg Sodium Valproate PhEur.
Epilim 200 Enteric Coated: 200 mg Sodium Valproate PhEur.
Epilim 100 mg Crushable: 100 mg Sodium Valproate PhEur.
Epilim Syrup and Liquid: 200 mg Sodium Valproate PhEur per 5 ml.

Pharmaceutical form
Epilim 500 Enteric Coated: Enteric coated tablets.
Epilim 200 Enteric Coated: Enteric coated tablets.
Epilim 100 mg Crushable: Tablets.
Epilim Syrup: Syrup.
Epilim Liquid: Liquid.

Clinical particulars

Therapeutic indications: In the treatment of generalised, partial or other epilepsy. In women of child bearing age, Epilim should be used only in severe cases or in those resistant to other treatment.

Posology and method of administration: Epilim tablets, syrup and liquid are for oral administration. Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency: It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see *Pharmacokinetic properties*).

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug related, porphyria.

Special warnings and special precautions for use:
Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone

bodies, this may give false positives in the urine testing of possible diabetics (see *Pregnancy and lactation, Undesirable effects*). In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml.

If it is necessary to dilute Epilim Syrup, the recommended diluent is syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life.

Interactions with other medicaments and other forms of interaction: Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate has appreciably less enzyme inducing effect than certain other anticonvulsants, and the efficacy of oral contraceptive agents does not appear to be affected.

Concurrent treatment with Epilim may affect the performance of some drugs and so clinical monitoring is recommended especially at the beginning of combined therapy.

1. The effects of neuroleptics, monoamine oxidase inhibitors, anti-depressants, and benzodiazepines may be potentiated.

2. Phenobarbitone plasma levels may increase and sedation may occur, particularly in children. The dose should be reduced immediately. Clinical monitoring is recommended throughout the first two weeks of combined treatment.

3. Phenytoin plasma levels, particularly of the free form, may increase following an initial decrease in total levels.

4. Primidone plasma levels may increase with exacerbation of adverse effects (such as sedation). The dose should be adjusted when appropriate.

5. The toxic effect of carbamazepine may be potentiated. Dosage should be adjusted when appropriate.

6. The metabolism of lamotrigine may be inhibited and the half life lengthened. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

7. Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.

8. Protein binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.

Concurrent treatment with some drugs may affect the performance of Epilim and dosage levels might need to be adjusted.

1. Anti-epileptic drugs with enzyme inducing effects (e.g. phenytoin, phenobarbitone, carbamazepine) may decrease valproate serum concentrations. Adjust dosage according to blood levels.

2. Felbamate may increase valproate serum concentration.

3. Cimetidine (but not ranitidine) and erythromycin may prolong the half-life and reduce clearance of valproate as a result of reduced hepatic metabolism.

4. Mefloquine may increase valproic acid metabolism. It also may have a convulsant effect. Seizures may occur in cases of combined therapy.

5. Cholestyramine may decrease the absorption of valproate.

6. Salicylates, e.g. aspirin, may displace valproate from protein binding sites.

Pregnancy and lactation: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound and other techniques if appropriate. There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contraindication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Effects on ability to drive and to use machines: Not applicable. Use of Epilim may provide seizure control such that the patient may again be eligible to hold a driving license.

Undesirable effects:

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidence mainly occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur, isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonaemia associated with neurological symptoms have been reported, in such cases further investigations should be considered. When an abnormality of the urea cycle is suspected (ornithine transcarbamylase deficiency), metabolic investigations should be performed. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis including, rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their pancreatic enzymes including serum amylase estimated; if these enzymes are elevated treatment should be discontinued.

Renal: There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Haematological: Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests, that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Appetite may increase and an increase in weight is not uncommon. Frequently at the start of treatment minor gastrointestinal irritation and, less commonly, nausea may occur. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Dermatological: Transient hair loss has often been noted in some patients. This effect does not appear to be dose related and regrowth normally begins within six months, although the hair may become more curly than previously. Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported. Rarely signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus. The occurrence of vasculitis has occasionally been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness. In massive overdose, i.e., with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Deaths have occurred following large overdoses. Hospital management of overdosage, including induced vomiting, gastric lavage, assisted ventilation and other supportive measures, is recommended. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Pharmacological properties

Pharmacodynamic properties: Sodium valproate is an anticonvulsant. The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Pharmacokinetic properties: The half life of sodium valproate is usually reported to be within the range 9 - 20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 -100 mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological or therapeutic effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Pre-clinical safety data: Not applicable.

Pharmaceutical particulars

List of excipients:

Enteric coated tablets: Polyvidone, croscarmellose sodium, microcrystalline cellulose, hydrated silica, polyvinylphthalate, lactose, talc, polyethylene glycol, citric acid monohydrate, hydroxypropyl methylcellulose, titanium dioxide (E171), colloidal anhydrous silica, alumina hydrate, sodium alginate, indigo carmine aluminium lake (E132), carmoisine aluminium lake (E122), beeswax, carnauba wax, polysorbate, water and sorbic acid.

Crushable tablets: Maize starch, kaolin light (naturall), silica hydrated, magnesium stearate and purified water†.

Epilim Syrup: Sorbitol powder, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, sodium saccharin, sucrose, flavour IFF cherry 740, Ponceau 4R (E124) and purified water.

Epilim Liquid: Hydroxyethyl cellulose, sorbitol powder, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, saccharin sodium, Ponceau 4R (E124), flavour IFF cherry 740, citric acid anhydrous and purified water.
(† not detected in final formulation.)

Incompatibilities: None.

Shelf life: Epilim Tablets and Syrup: 36 months. Epilim Liquid: 24 months.

Special precautions for storage:
Epilim Tablets: Store in a dry place below 30°C.
Epilim Syrup: Store below 30°C.
Epilim Liquid: Store below 30°C and away from direct sunlight. Epilim Liquid should not be diluted.

Nature and contents of container: Epilim Enteric Coated tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes of 100 and 112 tablets.

Epilim 100 mg Crushable Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes of 100 and 112 tablets.

Epilim Syrup and Liquid is supplied in amber glass bottles with polypropylene J-cap or aluminium tamper evident cap with extended polyethylene seal and amber polyethylene terephthalate bottles with polypropylene tamper evident closure. Bottle size 200 and 300 ml.

Instructions for use/handling: None.

Marketing authorisation numbers
Epilim 500 Enteric Coated 11723/0020.
Epilim 200 Enteric Coated 11723/0018.
Epilim Crushable 11723/0017.
Epilim Syrup 11723/0025.
Epilim Liquid 11723/0024.

Date of approval/revision of SPC September 1997.

Legal category POM.

EPILIM CHRONO®

Qualitative and quantitative composition
Epilim Chrono 200 Controlled Release tablets contain 133.2 mg Sodium Valproate PhEur and 58.0 mg Valproic Acid PhFr equivalent to 200 mg sodium valproate/tablet.
Epilim Chrono 300 Controlled Release tablets contain 199.8 mg Sodium Valproate PhEur and 87.0 mg Valproic Acid PhFr equivalent to 300 mg sodium valproate/tablet.
Epilim Chrono 500 Controlled Release tablets contain 333 mg Sodium Valproate PhEur and 145 mg Valproic Acid PhFr equivalent to 500 mg sodium valproate/tablet.

Pharmaceutical form Controlled release tablets.

Clinical particulars
Therapeutic indications: The treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Posology and method of administration: Epilim Chrono Controlled Release tablets are for oral administration.
Epilim Chrono is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.
Epilim Chrono may be given once or twice daily. The tablets should be swallowed whole and not crushed.
Daily dosage requirements vary according to age and body weight.

Monotherapy: Usual requirements are as follows:
Adults: Dosage should start at 600 mg daily increasing by 200 mg at three day intervals until control is achieved. This is generally within the dosage range 1000 mg to 2000 mg per day, i.e. 20–30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.
Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.
Children under 20 kg: An alternative formulation of Epilim should be used in this group of patients, due to the need for dose titration.
Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels. In patients with renal insufficiency it may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see *Pharmacokinetic properties*).
In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or modified release formulations on an equivalent daily dosage basis.

Combined therapy: When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.
NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug related, porphyria.

Special warnings and special precautions for use:
Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. (See *Pregnancy and lactation, Undesirable effects*).

Interactions with other medicaments and other forms of interaction: Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.
Valproate has appreciably less enzyme inducing effect than certain other anticonvulsants, and the efficacy of oral contraceptive agents does not appear to be affected.
Concurrent treatment with Epilim may affect the performance of some drugs and so clinical monitoring is recommended especially at the beginning of combined therapy.
1. The effects of neuroleptics, monoamine oxidase inhibitors, anti-depressants, and benzodiazepines may be potentiated.
2. Phenobarbitone plasma levels may increase and sedation may occur, particularly in children. The dose should be reduced immediately. Clinical monitoring is recommended throughout the first two weeks of combined treatment.
3. Phenytoin plasma levels, particularly of the free form, may increase following an initial decrease in total levels.
4. Primidone plasma levels may increase with exacerbation of adverse effects (such as sedation). The dose should be adjusted when appropriate.
5. The toxic effect of carbamazepine may be potentiated. Dosage should be adjusted when appropriate.
6. The metabolism of lamotrigine may be inhibited and the half-life lengthened. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.
7. Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.
8. Protein-binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.
Concurrent treatment with some drugs may affect the performance of Epilim and dosage levels might need to be adjusted.
1. Anti epileptic drugs with enzyme-inducing effects (e.g. phenytoin, phenobarbitone, carbamazepine) may decrease valproate serum concentrations. Adjust dosage according to blood levels.
2. Felbamate may increase valproate serum concentration.
3. Cimetidine (but not ranitidine) and erythromycin may prolong the half-life and reduce clearance of valproate as a result of reduced hepatic metabolism.
4. Mefloquine may increase valproic acid metabolism. It also may have a convulsant effect. Seizures may occur in cases of combined therapy.
5. Cholestyramine may decrease the absorption of valproate.
6. Salicylates, e.g. aspirin, may displace valproate from protein-binding sites.

Pregnancy and lactation: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.
The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1–2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound, and other techniques if appropriate.
There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme inducers.
Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Effects on ability to drive and to use machines: Not applicable. Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Undesirable effects: Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children, particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.
Clinical symptoms are more helpful than laboratory investigation in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis, e.g. prothrombin time, may be most relevant.
Routine measurement of liver function should be undertaken before therapy and periodically during the first six months, especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage.
Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time, should be monitored until they return to normal. However an abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they enter the same metabolic pathway.
Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonaemia associated with

neurological symptoms has also been reported. In such cases, further investigations should be considered. When an abnormality of the urea cycle is suspected (Ornithine transcarbamylase deficiency), metabolic investigations should be performed. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis including, rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their pancreatic enzymes including serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests, that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it has occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion, occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Appetite may increase and an increase in weight is not uncommon. Frequently at the start of treatment minor gastrointestinal irritation and, less commonly, nausea may occur. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Dermatological: Transient hair loss often has been noted in some patients. This effect does not appear to be dose-related and regrowth normally beings within six months, although the hair may become more curly than previously. Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus. The occurrence of vasculitus has occasionally been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Overdosage: Cases of accidental and suicidal valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentration 10 to 20 times maximum therapeutic levels, there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. A number of deaths have occurred following large overdoses. Hospital management of overdose including vomiting, gastric lavage, assisted ventilation and other supportive measures is recommended. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Pharmacological properties

Pharmacodynamic properties: Sodium valproate is an anticonvulsant. The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Pharmacokinetic properties: The half life of sodium valproate is usually reported to be within the range of 9–20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim Chrono may not be clearly correlated with the total of free (unbound) plasma valproic acid levels.

Epilim Chrono formulations are controlled release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (Cmax) and trough concentration (Cmin) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim EC.

Pre-clinical safety data: There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical particulars

List of excipients: Hydroxypropylmethyl cellulose, ethylcellulose, hydrated silica.

Film coat: Violet coat, containing titanium dioxide (E171), erythrosine BS (E127), indigo carmine (E132), iron oxide black (E172), hydroxypropylmethyl cellulose (E464), polyethylene glycol 400, purified water†. († Not detected in final formulation.)

Incompatibilities: None.

Shelf life: Epilim Chrono tablets have a shelf-life of 36 months.

Special precautions for storage: Store in a dry place below 30°C.

Nature and contents of container: Epilim Chrono Controlled Release tablets are supplied in blister packs further packed into a cardboard carton. Pack size 100 tablets.

Instructions for use/handling: Not applicable.

Marketing authorisation numbers

Epilim Chrono 200 Controlled Release 11723/0078
Epilim Chrono 300 Controlled Release 11723/0021
Epilim Chrono 500 Controlled Release 11723/0079

Date of approval/revision of SPC September 1997.

Legal category POM.

EPILIM® INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate PhEur 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections PhEur).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given *a slow intravenous injection over* 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Patients with renal insufficiency: It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

Combined therapy: When starting Epilim in patients already on other anticonvulsants these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see Further Information.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug-related. Porphyria.

Side-effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g. prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months especially in those who seem most at risk and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered. When an abnormality of the urea cycle is

suspected lamithine transcarbamylase deficiency), metabolic investigations should be performed. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis including rarely, fatalities occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Renal: There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Haematological: Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Prior to initiation of therapy and also before surgery, clinicians should assure themselves using the appropriate blood tests, that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, pancytopenia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal: Appetite may increase and an increase in weight is not uncommon. Frequently at the start of treatment, minor gastrointestinal irritation, and less commonly, nausea may occur. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported. Rarely signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus. The occurrence of vasculitis has occasionally been reported.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Drug interactions: Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate has appreciably less enzyme-inducing effect than certain other anticonvulsants, and the efficacy of oral contraceptive agents does not appear to be affected.

Concurrent treatment with Epilim may affect the performance of some drugs and so clinical monitoring is recommended especially at the beginning of combined therapy.

1. The effects of neuroleptics, monoamine oxidase inhibitors, anti-depressants, and benzodiazepines may be potentiated.

2. Phenobarbitone plasma levels may increase and sedation may occur, particularly in children. The dose should be reduced immediately. Clinical monitoring is recommended throughout the first two weeks of combined treatment.

3. Phenytoin plasma levels, particularly of the free form, may increase following an initial decrease in total levels.

4. Primidone plasma levels may increase with exacerbation of adverse effects (such as sedation). The dose should be adjusted when appropriate.

5. The toxic effect of carbamazepine may be potentiated. Dosage should be adjusted when appropriate.

6. The metabolism of lamotrigine may be inhibited and the half-life lengthened. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

7. Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.

8. Protein-binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.

Concurrent treatment with some drugs may affect the performance of Epilim and dosage levels might need to be adjusted.

1. Anti-epileptic drugs with enzyme-inducing effects (e.g. phenytoin, phenobarbitone, carbamazepine) may decrease valproate serum concentrations. Adjust dosage according to blood levels.

2. Felbamate may increase valproate serum concentration.

3. Cimetidine (but not ranitidine) and erythromycin may prolong the half-life and reduce clearance of valproate as a result of reduced hepatic metabolism.

4. Mefloquine may increase valproic acid metabolism. It also may have a convulsant effect. Seizures may occur in cases of combined therapy.

5. Cholestyramine may decrease the absorption of valproate.

6. Salicylates, e.g. aspirin, may displace valproate from protein-binding sites.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Pregnancy: An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) particularly of the limbs has been demonstrated in offspring born to mothers with epilepsy both untreated and treated including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1–2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound, and other techniques if appropriate.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers.

Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. Thus there appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Deaths have occurred following large overdoses. Hospital management of overdosage, including induced vomiting, gastric lavage, assisted ventilation and other supportive measures, is recommended. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Pharmaceutical precautions Epilim Intravenous freeze dried powder should be stored below 25°C. Infusion solutions at 2-8°C if stored before use, discarding any remaining after 24 hours. Epilim Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Legal category POM.

Package quantities Epilim Intravenous is supplied as a pack containing one vial of 400 mg Sodium Valproate PhEur and one ampoule containing 4 ml of solvent.

Further information The half life of sodium valproate is usually reported to be within the range 8–20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/litre (278–694 micro mol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Product licence numbers

Epilim Intravenous	11723/0022
Water for Injection	11723/0023

FORTAGESIC®

Presentation White tablets with bevelled edges 12.7 mm diameter, marked FORTAGESIC on one side. Each tablet provides Pentazocine BP 15 mg (as the hydrochloride) and Paracetamol PhEur 500 mg. Fortagesic tablets contain sodium metabisulphite.

Uses Fortagesic is a compound analgesic for the relief of moderate pain associated with musculoskeletal disorders or injuries, such as bursitis, sprains, strains, fibrositis, sciatica and osteoarthritis, and for rheumatoid arthritis in patients sensitive to aspirin.

Dosage and administration Fortagesic is for oral administration only.

Adults including the elderly: 2 tablets up to four times daily.

Children: 7–12 years: 1 tablet every three to four hours. Not more than 4 doses to be taken in any 24 hour period. Not recommended for children under 7 years of age.

Contra-indications, warnings, etc

Contra-indications: Fortagesic should not be administered to patients with established respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and is also contraindicated in the presence of acute alcoholism, head injuries, conditions in which intracranial pressure is raised, acute bronchial asthma, in heart failure, secondary to chronic lung disease and in patients known to be hypersensitive to pentazocine or paracetamol.

Warnings:

Use in pregnancy and lactation: There is epidemiological evidence for the safety of paracetamol in human pregnancy. No such evidence exists for pentazocine (other than during labour) but it has been widely used for many years without apparent ill consequences. In rodents, harmful effects in the foetus have been observed but only at doses high enough to cause maternal toxicity. Pentazocine can readily cross the placental barrier and enter the foetal circulation and has the potential to cause opioid effects including central depression and abstinence syndrome in the foetus and new born infant (see below). It does not appear to have significant adverse effects on uterine function at parturition. Nonetheless, careful consideration should be given to the use of Fortagesic during pregnancy, particularly during the first trimester, or at term.

Special attention should be paid to clinical monitoring of the newborn, particularly premature infants, if pentazocine has been used during labour. Pentazocine is excreted in very small amounts in breast milk. Caution should therefore be observed in administering pentazocine to breast feeding mothers particularly of infants at risk.

Precautions:

Particular caution should be observed in administering Fortagesic to patients with porphyria, since it may provoke an acute attack in susceptible individuals, as well as in its use in patients who are receiving

10000600

SUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of Medicinal Product

Epilim 200 Enteric Coated

2. Qualitative and Quantitative Composition

Epilim 200 Enteric Coated Tablets contain 200mg of Sodium Valproate

3. Pharmaceutical Form

Enteric coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and Method of Administration

Epilim 200 Enteric Coated Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Monotherapy
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg

20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties.)

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, eg phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Hypersensitivity to sodium valproate. Active liver disease; family history of severe hepatic dysfunction, particularly drug related; porphyria.

4.4 Special Warnings and Special Precautions for Use

Hepatic: Routine measurement of liver function should be undertaken before therapy and periodically during the first 6 months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision (see also section 4.8 Undesirable Effects).

Haematological: Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests (blood cell count, bleeding time and

coagulation tests), that there is no undue potential for bleeding complications (see also section 4.8 Undesirable Effects).

Pancreatitis: Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting). Medical evaluation (including measurement of serum amylase) should be undertaken in patients presenting with symptoms suggestive of pancreatitis and Epilim should be discontinued if pancreatitis is diagnosed.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain.

Pregnancy: It is recommended that Epilim be used in women of child-bearing age only in severe cases or those resistant to other treatment because of the potential teratogenic risk to the foetus exposed to valproate *in utero*. Women of child-bearing age should be informed of the potential risks and benefits of continuing anti-epileptic treatment throughout pregnancy (see also section 4.6 Pregnancy and Lactation).

Systemic lupus erythematosus: Caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus because, rarely, signs of an immune disorder have occurred (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

4.5.1 Effects of Valproate on Other Drugs

- Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- Phenobarbital

Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

- ***Zidovudine***

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***

Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of Other Drugs on Valproate

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

Both ***mefloquine*** and ***chloroquine*** may lower the seizure threshold. In addition, mefloquine may decrease valproate levels. The dosage of Epilim may need adjustment accordingly.

In case of concomitant use of valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics may reduce plasma valproic acid to sub-therapeutic levels. If these antibiotics have to be administered, close monitoring of valproic acid plasma levels is recommended.

Cholestyramine may decrease the absorption of valproate.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Epilim does not significantly induce hepatic enzymes; the efficacy of oral contraceptive agents does not appear to be affected.

4.6 Pregnancy and Lactation

An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding

The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contraindication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

4.7 Effects on Ability to Drive and to Use Machines

Use of Epilim may provide seizure control such that the patient may again be eligible to hold a driving licence.

However, patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

4.8 Undesirable Effects

Hepatic
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis eg prothrombin time may be most relevant.

Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Metabolic
Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4 Special Warnings and Special Precautions for Use). Oedema has been rarely reported.

Pancreatic
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Renal
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Haematological
Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological
Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal
Appetite may increase and Epilim very commonly causes weight gain which may be marked and progressive (see section 4.4 Special Warnings and Special Precautions for Use). Frequently at the start of treatment minor gastrointestinal irritation and, less commonly, nausea may occur. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Dermatological
Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported.

Endocrine
There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Others
The occurrence of vasculitis has occasionally been reported. Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

4.9 Overdosage

Cases of accidental and deliberate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, ie, with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. However, the symptoms may be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cerebral oedema and intracranial hypertension have been reported. Deaths have occurred following large overdoses.

Hospital management of overdosage, including induced vomiting, gastric lavage, assisted ventilation and other supportive measures, is recommended.

Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic Properties

The half-life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and

presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical Safety Data

Not applicable.

6. Pharmaceutical Particulars

6.1 List of Excipients

Povidone, talc, calcium silicate, magnesium stearate, hypromellose 6, citric acid anhydrous, macrogel 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, violet lake solids, industrial methylated spirits, purified water.

6.2 Incompatibilities

There are no major incompatibilities.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and Contents of Container

Epilim 200 Enteric Coated Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Instructions for Use / Handling

None.

10000609

7. **Marketing Authorisation Holder**

Sanofi Winthrop Ltd (*trading as Sanofi Winthrop*)
One Onslow Street
Guildford
Surrey GU1 4YS

or trading as:

Sanofi-Synthelabo
PO Box 597
Guildford
Surrey

8. **Marketing Authorisation Number**

PL 11723/0018

9. **Date of Renewal of Authorisation**

18 June 1993/12 May 1995

10. **Date of Revision of Text**

March 2001

10000578

cSUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of Medicinal Product

Epilim 200 Enteric Coated

2. Qualitative and Quantitative Composition

Epilim 200 Enteric Coated Tablets contain 200mg of Sodium Valproate

3. Pharmaceutical Form

Enteric coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and Method of Administration

Epilim 200 Enteric Coated Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Monotherapy
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg

20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties.)

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, eg phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Hypersensitivity to sodium valproate. Active liver disease; family history of severe hepatic dysfunction, particularly drug related; porphyria.

4.4 Special Warnings and Special Precautions for Use

Hepatic: Routine measurement of liver function should be undertaken before therapy and periodically during the first 6 months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision (see also section 4.8 Undesirable Effects).

Haematological: Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using the appropriate blood tests (blood cell count, bleeding time and coagulation tests), that there is no undue potential for bleeding complications (see also section 4.8 Undesirable Effects).

Pancreatitis: Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting). Medical evaluation (including measurement of serum amylase) should be undertaken in patients presenting with symptoms suggestive of pancreatitis and Epilim should be discontinued if pancreatitis is diagnosed.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain.

Systemic lupus erythematosus: Caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus because, rarely, signs of an immune disorder have occurred (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

4.5.1 Effects of Valproate on Other Drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Phenobarbital***

Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

- ***Zidovudine***
Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 **Effects of Other Drugs on Valproate**
Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

Both ***mefloquine*** and ***chloroquine*** may lower the seizure threshold. In addition, mefloquine may decrease valproate levels. The dosage of Epilim may need adjustment accordingly.

In case of concomitant use of valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics may reduce plasma valproic acid to sub-therapeutic levels. If these antibiotics have to be administered, close monitoring of valproic acid plasma levels is recommended.

Cholestyramine may decrease the absorption of valproate.

4.5.3 **Other Interactions**
Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Epilim does not significantly induce hepatic enzymes; the efficacy of oral contraceptive agents does not appear to be affected.

4.6 Pregnancy and Lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

- Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

- Risk associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.

Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should

be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

- ***Risk in the neonate***

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

4.7 Effects on Ability to Drive and to Use Machines

Use of Epilim may provide seizure control such that the patient may again be eligible to hold a driving licence.

However, patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

4.8 Undesirable Effects

Hepatic

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis eg prothrombin time may be most relevant.

Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires

cessation of treatment. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Metabolic
Hyperammonaemia without changes in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4 Special Warnings and Special Precautions for Use). Oedema has been rarely reported.

Pancreatic
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Renal
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Haematological
Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia, leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological
Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Gastrointestinal

Appetite may increase and Epilim very commonly causes weight gain which may be marked and progressive (see section 4.4 Special Warnings and Special Precautions for Use). Frequently at the start of treatment minor gastrointestinal irritation and, less commonly, nausea may occur. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Dermatological
Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported.

Endocrine
There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Others
The occurrence of vasculitis has occasionally been reported. Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

4.9 Overdosage

Cases of accidental and deliberate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, ie, with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. However, the symptoms may be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cerebral oedema and intracranial hypertension have been reported. Deaths have occurred following large overdoses.

Hospital management of overdosage, including induced vomiting, gastric lavage, assisted ventilation and other supportive measures, is recommended.

Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic Properties

The half-life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical Safety Data

Not applicable.

6. Pharmaceutical Particulars

6.1 List of Excipients

Povidone, talc, calcium silicate, magnesium stearate, hypromellose 6, citric acid anhydrous, macrogel 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, violet lake solids, industrial methylated spirits, purified water.

6.2 Incompatibilities

There are no major incompatibilities.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and Contents of Container

Epilim 200 Enteric Coated Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Instructions for Use / Handling

None.

7. Marketing Authorisation Holder

Sanofi-Synthelabo Limited (*trading as Sanofi Winthrop*)
One Onslow Street
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Surrey GU1 4YS

or trading as:

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PO Box 597
Guildford
Surrey

8. Marketing Authorisation Number

PL 11723/0018

9. Date of Renewal of Authorisation

17 July 2000

10. Date of Revision of Text

April 2003

Summary of Product Characteristics

1. Name of the medicinal product

Epilim 200 Enteric Coated

2. Qualitative and quantitative composition

Epilim 200 Enteric Coated Tablets contain 200mg of Sodium Valproate

3. Pharmaceutical form

Enteric coated tablets.

4. Clinical Particulars

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

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Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Adminstration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice.
Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interactions with other medicinal products and other forms of interactions

4.5.1 Effects of Epilim on other drugs

- Antipsychoticss, MAO inhibitors, antidepressants and benzodiazepines
Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Phenobarbital
Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Epilim may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

- ***Zidovudine***

Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***

Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Epilim may increase valproic acid plasma concentration. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***imipenem, panipenem*** and ***meropenem***: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Colestyramine may decrease the absorption of Epilim.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Use during pregnancy and lactation

Women of childbearing potential should not be started on Epilim without specialist neurological advice.

Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.

Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.

If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.

When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of Epilim during pregnancy has been described as follows:

- Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to Epilim and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

- Risk associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate.

Some data from studies, of women with epilepsy, have suggested an association between in-utero exposure to valporate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, Epilim anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of Epilim in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on Epilim.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and Lactation)
Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Warnings) Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Very rare cases of hyponatraemia have been reported.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation).

Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders:
Cutaneous reactions such as exanthematous rash rarely occur with Epilim. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders:
Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Special Precautions for Use).

4.9 Overdose symptoms, emergency procedures, antidotes

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties).
Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Sodium valproate is an anticonvulsant.

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of Excipients

Povidone, talc, calcium silicate, magnesium stearate, hypromellose 6, citric acid anhydrous, macrogel 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, violet lake solids (containing titanium dioxide, amaranth lake, indigo carmine lake and hydroxypropyl cellulose), industrial methylated spirits, purified water.

6.2 Major incompatibilities

There are no major incompatibilities.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Enteric Coated Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Special precautions for disposal

None.

7. Marketing authorisation holder

Sanofi-Synthelabo Limited (*trading as Sanofi Winthrop*)
One Onslow Street
Guildford
Surrey GU1 4YS

or trading as:

Sanofi-Synthelabo
PO Box 597
Guildford
Surrey

8. Marketing authorisation number

PL 11723/0018

9. Date of the first authorisation or renewal

17 July 2000

10. Date of revision of the text

18 October 2005

11. Legal classification

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Enteric Coated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Sodium Valproate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Enteric coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Enteric Coated Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg

body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Women of childbearing potential (see section 4.6): A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child . This decision is to be taken;

before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation).

Suicidal ideation and behaviour: Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- Antipsychoticss, MAO inhibitors, antidepressants and benzodiazepines
Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Phenobarbital
Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine
Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine
The risk of rash associated with the use of Epilim may be increased if lamotrigine is also administered. Epilim may reduce lamotrigine metabolism

and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***
Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Epilim may increase valproic acid plasma concentration. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***imipenem, panipenem*** and ***meropenem***:
Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Colestyramine may decrease the absorption of Epilim.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Pregnancy and lactation

Women of childbearing potential should not be started on Epilim without specialist neurological advice.

Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.

Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.
If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.

When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

4.6.1 Pregnancy

- Risk associated with epilepsy and antiepileptics
In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with seizures
During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).

*- **Risk in the neonate***
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of Epilim in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Epilim, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Warnings) Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Very rare cases of hyponatraemia have been reported.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including red cell aplasia.
Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders:
Rash rarely occurs with Epilim. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), but the mode of action is as yet unclear.
Very rare cases of enuresis have been reported.

Immune system disorders:
Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Special Precautions for Use).

4.9 Overdose

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties).

Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-*

vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid anhydrous (E330)
Macrogol 6000
Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)
Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Enteric Coated Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis
One Onslow Street
Guildford
Surrey GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11723/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

01 October 2010

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Enteric Coated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Sodium Valproate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Enteric coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Enteric Coated Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg

body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when

a women of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential

regarding the risks associated with pregnancy - because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Lithium

Epilim has no effect on serum lithium levels

- Phenobarbital

Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone

Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin

Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine

Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine

Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***

Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***

Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***

Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Epilim decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.
In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***imipenem, panipenem*** and ***meropenem***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Colestyramine may decrease the absorption of Epilim.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential should not be started on Epilim without specialist neurological advice.
Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.
Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.
If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.
When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

4.6.1 Pregnancy

- Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.
No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with seizures
During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.
There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.
Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy.

If a women plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication:

- In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the

risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.

- In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.
- Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.
Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

4.6.2 Lactation

Excretion of Epilim in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Epilim, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver injury (see section 4.4.1 Warnings) Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of extrapyramidal symptoms which may not be reversible including reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder: Confusion has been reported

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Very rare cases of hyponatraemia have been reported.
Syndrome of inappropriate secretion of ADH (SIADH)

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including pure red cell aplasia.
Agranulocytosis.

Isolated finding of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders:
Rash rarely occurs with valproate. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and dysmenorrhea have been reported. Very rarely gynaecomastia has occurred. Male infertility.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), but the mode of action is as yet unclear.
Very rare cases of enuresis have been reported.

Immune system disorders:
Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Special Precautions for Use).

4.9 Overdose

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties).

Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid anhydrous (E330)
Macrogol 6000
Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)

Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Enteric Coated Tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis
One Onslow Street
Guildford
Surrey GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

13 July 2011

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Sodium Valproate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

Lilac coloured circular biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Gastro-resistant tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with

anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- Antipsychoticss, MAO inhibitors, antidepressants and benzodiazepines
Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Lithium
Epilim has no effect on serum lithium levels

- Phenobarbital
Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical

monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***

Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***
Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Epilim decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.
In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***imipenem, panipenem*** and ***meropenem***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels should be performed.
Colestyramine may decrease the absorption of Epilim.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential should not be started on Epilim without specialist neurological advice.

Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.

Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.

If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.

When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

4.6.1 Pregnancy

- Risk associated with epilepsy and antiepileptics
In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with seizures
During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73% (95% CI: 8.16 – 13.29). Available data indicate dose dependency of this effect.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data

The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a woman of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy.

If a woman plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication:

- In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.
- In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.
- Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors; afibrinogenemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

4.6.2 Lactation

Excretion of Epilim in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Epilim, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common $\geq$ 1 %; Common $\geq$ 1 and $\leq$ 10 %; Uncommon $\geq$ 0.1 and $\leq$ 1 %; Rare $\geq$ 0.01 and $\leq$ 0.1 %; Very rare $\geq$ 0.01 %, Unknown (cannot be estimated from available data).

Congenital and familial/genetic disorders: (see section 4.6 Fertility, pregnancy and lactation)

Hepato-biliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders
Very common: nausea,
Common: gastralgia, diarrhoea

The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim (Epilim Gastro-resistant tablets).

Uncommon: pancreatitis, sometimes lethal, (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus,
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder:
Common: confusional state, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolic disorders:
Common: hyponatraemia.
Rare: hyperammonaemia* (see section 4.4.2 Precautions)

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions).
Uncommon: pancytopenia, leucopenia

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia,
agranulocytosis, anaemia macrocytic, macrocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and or dose related alopecia (hair loss).
Regrowth normally begins within six months, although the hair may become more curly than previously.

Uncommon: angioedema, rash

Hirsutism and acne have been very rarely reported.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation).
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: Deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Rare: enuresis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: non-severe oedema peripheral

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Common: Weight increased*
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4.2 Precautions)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

4.9 Overdose

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic

acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties).
Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.
In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An

increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid anhydrous (E330)
Macrogol 6000
Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)
Violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Gastro-resistant tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

28 November 2012

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Sodium Valproate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

Lilac coloured circular biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Gastro-resistant tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage

Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Female children, female adolescents, women of childbearing potential and pregnant women

Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.
These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy (see section 4.6).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be

weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- Antipsychoticss, MAO inhibitors, antidepressants and benzodiazepines
Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Lithium
Epilim has no effect on serum lithium levels

- Phenobarbital
Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***

Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***

Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***

Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Epilim decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.
In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***imipenem, panipenem*** and ***meropenem***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels should be performed.
Colestyramine may decrease the absorption of Epilim.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children, female adolescents and woman of childbearing potential (see above and section 4.4)

If a Woman wants to plan a Pregnancy

- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.
- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.
- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

<u>Risk in the neonate</u>
- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a

decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/ 10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from available data).

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepato-biliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders
Very common: nausea,
Common: gastralgia, diarrhoea

The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food or by using Enteric Coated Epilim (Epilim Gastro-resistant tablets).

Uncommon: pancreatitis, sometimes lethal, (see section 4.4 Special Warnings and Special Precautions for Use).

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus,
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder:
Common: confusional state, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolic disorders:
Common: hyponatraemia.
Rare: hyperammonaemia* (see section 4.4.2 Precautions)

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions).
Uncommon: pancytopenia, leucopenia

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia,
agranulocytosis, anaemia macrocytic, macrocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and or dose related alopecia (hair loss).
Regrowth normally begins within six months, although the hair may become more curly than previously.

Uncommon: angioedema, rash

Hirsutism and acne have been very rarely reported.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation).
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: Deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Rare: enuresis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: non-severe oedema peripheral

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Common: Weight increased*
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4.2 Precautions)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Cases of accidental and deliberate Epilim overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties).
Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.
In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid monohydrate (E330)
Macrogol 6000
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Gastro-resistant tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

Or trading as:

sanofi-aventis or Sanofi
One Onslow Street
Guildford

Surrey
GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

11 February 2015

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of Sodium Valproate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

Lilac coloured circular biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Gastro-resistant tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults

Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 mg – 2000 mg per day, i.e. 20 – 30 mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg
Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg
20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2, Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Female children and women of childbearing potential
Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Combined Therapy
When starting Epilim in patients already on other anti-convulsants, these should be tapered slowly: initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 – 10 mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Epilim is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Hypersensitivity to sodium valproate.
- Porphyria.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has

advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:
Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Epilim is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without

interruption during the entire duration of treatment with valproate.

- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist
The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:
- The Patient Card is provided with every valproate dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy.

Aggravated convulsions:
As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data does not exclude the possibility of an increased risk for sodium valproate.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

4.4.2 Precautions

Haematological:
Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus:
Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim (see section 4.3).

Weight gain:
Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Diabetic patients:
Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Epilim.

Alcohol:
Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
  Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.

  In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Lithium***
  Epilim has no effect on serum lithium levels.

- ***Olanzapine***
  Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***
  Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
  Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is

recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
  Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
  Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
  Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
  Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Rufinamide***
  Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***
  Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***
  Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***
  In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Vitamin K-dependent anticoagulants***
  The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
  Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

Anti-epileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with ***phenytoin*** or ***phenobarbital***. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of ***felbamate*** and Epilim decreases valproic acid clearance by 22% – 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

In case of concomitant use of Epilim and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics such as ***panipenem, imipenem*** and ***meropenem***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60% – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels should be performed.

Protease inhibitors such as ***lopinavir*** and ***ritonavir*** decrease valproate plasma level when co-administered.

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***
  Co-administration of Epilim and quetiapine may increase the risk of neutropenia/leucopenia.

Epilim usually has no enzyme-inducing effect; as a consequence, Epilim does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30 – 40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and section 4.4)

If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations (see section 4.2).

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate

supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤

1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food.
Uncommon: pancreatitis, sometimes lethal (see section 4.4 Special Warnings and Special Precautions for Use)

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:
Common: hyponatraemia, weight increased*
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).
Rare: hyperammonaemia* (see section 4.4.2 Precautions), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions)
Uncommon: pancytopenia, leucopenia

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation)
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Cases of accidental and deliberate Epilim overdose have been reported. At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and

circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Epilim formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The half-life of Epilim is usually reported to be within the range 8 – 20 hours. It is usually shorter in children.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 – 100 mg/litre (278 – 694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between

6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid monohydrate (E330)
Macrogol 6000
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Gastro-resistant tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 100 and 112 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
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UK

Or trading as:

sanofi-aventis or Sanofi
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8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

30/04/2018

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Epilim 200 Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of Sodium Valproate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

Lilac coloured circular biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and method of administration

Epilim 200 Gastro-resistant tablets are for oral administration.

Daily dosage requirements vary according to age and body weight. Epilim tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:

Adults
Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000 – 2000 mg per day, i.e.

20 – 30 mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg
Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg
20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly
Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Epilim since they employ the same metabolic pathway (see sections 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 and 4.4).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1).

Female children and women of childbearing potential
Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Combined Therapy

When starting Epilim in patients already on other anti-convulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 – 10 mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

4.3 Contraindications

Epilim is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see sections 4.4 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Hypersensitivity to sodium valproate.
- Porphyria.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and in particular young

children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:
Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Epilim should be discontinued.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme
Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Epilim is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.

- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:
- The Patient Card is provided with every valproate dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy.

Aggravated convulsions:
As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data does not exclude the possibility of an increased risk for sodium valproate.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

4.4.2 Precautions

Haematological tests:
Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 and 5.2).

Patients with systemic lupus erythematosus:
Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see section 4.8).

Urea cycle disorders:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim (see section 4.3).

Weight gain:
Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8).

Diabetic patients:
Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Carnitine palmitoyltransferase (CPT) type II deficiency:
Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Epilim.

Alcohol:
Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Epilim on other drugs

- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
  Epilim may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.

  In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Lithium***
  Epilim has no effect on serum lithium levels.

- ***Olanzapine***
  Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***
  Epilim increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
  Epilim increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is

recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
  Epilim decreases phenytoin total plasma concentration. Moreover Epilim increases phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
  Clinical toxicity has been reported when Epilim was administered with carbamazepine as Epilim may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
  Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
  Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Rufinamide***
  Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***
  Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***
  Epilim may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***
  In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Temozolomide***
  Co-administration of temozolomide and Epilim may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Epilim

- ***Anti-epileptics***
  Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

  Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

  On the other hand, combination of felbamate and Epilim decreases valproic acid clearance by 22% – 50% and consequently increase the valproic acid plasma concentrations. Epilim dosage should be monitored.

- ***Anti-malarial agents***
  Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

- ***Highly protein bound agents***
  In case of concomitant use of Epilim and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased.

- ***Vitamin K-dependent factor anticoagulants***
  The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Cimetidine or erythromycin***
  Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

- ***Carbapenem antibiotics (such as panipenem, imipenem and meropenem)***
  Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60% – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels should be performed.

- ***Rifampicin***
  Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors***
  Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered.

- ***Cholestyramine***

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

- ***Oestrogen-containing products, including oestrogen-containing hormonal contraceptives***
  Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

  On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

4.5.3 Other interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***
  Co-administration of Epilim and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2

– 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30 – 40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and section 4.4)

Oestrogen-containing products
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations (see section 4.2).

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food.
Uncommon: pancreatitis, sometimes lethal (see section 4.4 Special Warnings and Special Precautions for Use)

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:
Common: hyponatraemia, weight increased*
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).
Rare: hyperammonaemia* (see section 4.4.2 Precautions), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions)
Uncommon: pancytopenia, leucopenia

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation)
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Cases of accidental and deliberate Epilim overdose have been reported. At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Epilim formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, ATC Code: N03AG01

The most likely mode of action for Epilim is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 – 100 mg/litre (278 – 694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Metabolism
The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

The half-life of Epilim is usually reported to be within the range 8 – 20 hours. It is usually shorter in children.

Interaction with oestrogen-containing products
Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone (E1201)
Talc
Calcium silicate (E552)
Magnesium stearate (E572)

Tablet subcoat:
Hypromellose (E464)
Citric acid monohydrate (E330)
Macrogol 6000
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

Enteric coat:
Polyvinyl acetate phthalate
Diethyl phthalate
Stearic acid (E570)
Titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim 200 Gastro-resistant tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes 30, 100 and 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

Or trading as:

sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1993
Date of latest renewal: 28 May 2004

10 DATE OF REVISION OF THE TEXT

31/08/2018

LEGAL STATUS

POM

Epilim – patient information leaflets

40028462

What you should know about

Epilim® Enteric Coated

Sodium Valproate BP

Please read this carefully before you start to take your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of your medicine is Epilim. It contains Sodium Valproate. This is one of a group of medicines called "anticonvulsant or anti-epileptic agents" which are used to treat epilepsy.

Things to remember about Epilim

1. **Before taking your medicine read the back of this leaflet.**
2. **Take your medicine as directed by your doctor. Read the instructions on the label carefully.**
3. **Epilim can sometimes cause side effects. See "After taking your medicine" on the back of this leaflet.**
4. **Do not stop taking your medicine suddenly. Ask your doctor first.**
5. **Tell medical staff you are taking this medicine, for example, if you go into hospital or see a dentist or another doctor.**
6. **If you are likely to become pregnant, tell your doctor.**

You will find more about Epilim on the back of this leaflet.

Continued from overleaf

BEFORE TAKING YOUR MEDICINE

If you have liver disease DO NOT take Epilim without first talking to your doctor again.

If you can answer YES to any of the following questions tell your doctor. He may need to give you special instructions.

Are you pregnant or likely to become pregnant?

Are you diabetic?

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Are you taking any other medicines to control your epilepsy?

Are you taking any medicine to reduce blood clotting (eg anticoagulant, aspirin)?

Are you taking antidepressants?

TAKING YOUR MEDICINE

Take your medicine regularly, as directed by your doctor. This is particularly important with anticonvulsants to make sure that you are getting the best control from your medication.

Look at the label on your medicine. It will tell you when to take it. If it does not, or you are not sure, ask your doctor or pharmacist for advice.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the correct time take it as soon as you remember then go on as before.

If you accidentally take an overdose contact your nearest hospital casualty department or tell your doctor immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

AFTER TAKING YOUR MEDICINE

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, loss of appetite, jaundice or worsening of your epilepsy.

Epilim may sometimes cause minor stomach upset, increased appetite or weight gain. You need only consult your doctor about these if symptoms become troublesome.

Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before.

Epilim can also have other effects. You should report any of the following symptoms to your doctor.

- Severe stomach pains
- Abnormal bleeding or a tendency to bruise more easily
- Shakiness or problems with balance
- A rash or anything else which is unusual or unexpected

Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

STORING YOUR MEDICINE

Keep your tablets in a safe place where children cannot reach them; your tablets could harm them.

Keep your tablets in the protective foil until you are ready to take them. If you remove them from the foil too soon they will spoil!

If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist. Only keep them if your doctor tells you to.

WHAT'S IN YOUR MEDICINE

Epilim Enteric-Coated tablets are lilac and come in two sizes containing 200mg or 500mg Sodium Valproate. They contain colour and other inactive ingredients including E123 (Amaranth).

This leaflet provides a summary of the information available on your medicine. For further information, consult your doctor or pharmacist.

THIS LEAFLET APPLIES TO EPILIM ENTERIC COATED TABLETS ONLY

REMEMBER: This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet has been prepared in accordance with guidelines issued by the Association of the British Pharmaceutical Industry.

Made in England by:
Sanofi Winthrop Ltd
One Onslow Street
Guildford, Surrey
GU1 4YZ

Sanofi Winthrop Ireland Ltd
Putery Road
Dun Laoghaire
Ireland

SANOFI WINTHROP

10016594

EPILIM ENTERIC COATED TABLETS
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of this medicine is Epilim Enteric Coated tablets.

What is in this medicine?

Each Epilim 200 tablet contains 200mg Sodium Valproate PhEur.

Each Epilim 500 tablet contains 500mg Sodium Valproate PhEur.

Each tablet also contains povidone, calcium silicate, talc, magnesium stearate, hypromellose, citric acid, polyethylene glycol, violet lake, polyvinyl acetate phthalate, diethyl phthalate, and stearic acid.

Epilim tablets are gluten free.

Epilim tablets are round lilac coloured tablets and are supplied in cartons of 100.

Epilim is an antiepileptic.

The Product Licence holder is:-

Sanofi Winthrop Ltd
One Onslow Street
Guildford
Surrey
GU1 4YS

The manufacturer is:-

Sanofi Winthrop Ltd
Edgefield Avenue
Fawdon
Newcastle Upon Tyne
NE3 3TT

What is this medicine for?

Epilim is used to treat epilepsy (fits). Doctors sometimes prescribe this medicine for other purposes; ask your doctor for information.

Before taking this medicine.

Epilim should not be taken by patients with liver problems, those with a family history of liver problems or those with a known allergy to Epilim/sodium valproate.

If you are diabetic Epilim may make urine tests give false results.

Epilim and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

Breast feeding: - very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors.
- anticoagulant therapy - used to thin the blood (eg warfarin)
- other anticonvulsant therapy eg. phenytoin, carbamazepine, phenobarbitone, lamotrigine.
- cimetidine - used to treat stomach ulcers
- aspirin
- antacids - used to treat ingestion

Taking this medicine.

Adults:- The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity should be divided and taken in 2 separate doses.

Children over 20kg:- The usual dose of Epilim is based on the childs weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity should be divided and given in 2 separate doses.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.

If you have severe kidney disease your doctor may prescribe a lower dose.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the right time take it as soon as you remember then go on as before.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Whilst taking this medicine.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver (and very rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, loss of appetite, jaundice, swelling of the legs or worsening of your epilepsy. Your doctor may wish to do tests before you start treatment and for the first six months of treatment. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may also cause tiredness; confusion; hallucinations; change in mood; jerky muscle movements, rashes, and loss of consciousness. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred: if you have lupus, please tell your doctor before taking Epilim.

Do not use this medicine after the expiry date which you will find on the pack.

Epilim tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

10018597

Date of last revision August 1994.

This leaflet does not contain all the information about your medicine. Pharmaceutical companies are not able to discuss your personal medical case. If you have any questions or are not sure about anything ask your doctor or pharmacist.

10000755

LEAFLET WITH VARIATIONS DATED/ APPROVED 26/3/96

EPILIM ENTERIC COATED TABLETS
(Sodium valproate)
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of this medicine is Epilim Enteric Coated tablets.

What is in this medicine?

Each Epilim 200 EC tablet contains 200mg Sodium Valproate PhEur.

Each Epilim 500 EC tablet contains 500mg Sodium Valproate PhEur.

Each tablet also contains lactose, polyvidone, croscarmellose sodium, microcrystalline cellulose, hydrated silica, polyvinyl acetate phthalate, talc, polyethylene glycol, citric acid, hydroxypropyl methylcellulose, titanium dioxide, colloidal anhydrous silica, alumina hydrate, sodium alginate, indigo carmine aluminium lake, carmoisine aluminium lake, beeswax, carnauba wax, polysorbate, water and sorbic acid.

Epilim tablets are round lilac coloured tablets and are supplied in cartons of 100 or 112. *(final printed version to include only marketed pack sizes)*

Epilim is an antiepileptic.

The Product Licence/Authorisation holder is:-

UK
Sanofi Winthrop Ltd
One Onslow Street
Guildford
Surrey
GU1 4YS

Ireland
Sanofi Winthrop Ireland Ltd
United Drug House
Belgard Road
Tallaght
Dublin 24

The manufacturer is:-

Sanofi Winthrop Ltd
Edgefield Avenue
Fawdon
Newcastle Upon Tyne
NE3 3TT
UK

What is this medicine for?

Epilim is used to treat epilepsy (fits).

Before taking this medicine.

Epilim should not be taken by patients with:-

- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria

If you are diabetic Epilim may make urine tests give false results.

Epilim and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

Breast feeding: - very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors.
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine.
- cimetidine - used to treat stomach ulcers
- aspirin
- erythromycin - an antibiotic
- mefloquine - used to prevent malaria

Taking this medicine.

Adults:-	The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity should be divided and taken in 2 separate doses e.g. half in the morning and half in the evening.
Children over 20kg:-	The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Children under 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is 20mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.

If you have severe kidney disease your doctor may prescribe a lower dose.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the right time take it as soon as you remember then go on as before.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Whilst taking this medicine.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, loss of appetite, jaundice, swelling of the legs or worsening of your epilepsy. Your doctor may wish to do tests before you start treatment and for the first six months of treatment. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may also cause tiredness; confusion; hallucinations; change in mood; jerky muscle movements, rashes, and loss of consciousness. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred: if you have lupus, please tell your doctor before taking Epilim.

Do not use this medicine after the expiry date which you will find on the pack.

Epilim tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Date of last revision July 1996

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

10000726

CPIT Variation

EPILIM ENTERIC COATED TABLETS
(Sodium valproate)
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of this medicine is Epilim Enteric Coated tablets.

What is in this medicine?

Each Epilim 200 EC tablet contains 200mg Sodium Valproate PhEur.

Each Epilim 500 EC tablet contains 500mg Sodium Valproate PhEur.

Each tablet also contains lactose, polyvidone, croscarmellose sodium, microcrystalline cellulose, hydrated silica, polyvinyl acetate phthalate, talc, polyethylene glycol, citric acid, hydroxypropyl methylcellulose, titanium dioxide, colloidal anhydrous silica, alumina hydrate, sodium alginate, indigo carmine aluminium lake, carmoisine aluminium lake, beeswax, carnauba wax, polysorbate, water and sorbic acid.

Epilim tablets are round lilac coloured tablets and are supplied in cartons of 100 or 112. *(final printed version to include only marketed pack sizes)*

Epilim is an antiepileptic.

The Product Licence/Authorisation holder is:-

UK
Sanofi Winthrop Ltd
One Onslow Street
Guildford
Surrey
GU1 4YS

Ireland
Sanofi Winthrop Ireland Ltd
United Drug House
Belgard Road
Tallaght
Dublin 24

The manufacturer is:-

Sanofi Winthrop Ltd
Edgefield Avenue
Fawdon
Newcastle Upon Tyne
NE3 3TT
UK

What is this medicine for?

Epilim is used to treat epilepsy (fits).

10000727

Before taking this medicine.

Epilim should not be taken by patients with:-

- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria

If you are diabetic Epilim may make urine tests give false results.

Epilim and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. **There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy.** It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

Breast feeding: - very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors.
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, **primidone, felbamate**.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin - an antibiotic
- mefloquine - used to prevent malaria
- **benzodiazepines - used as sleeping tablets and to treat anxiety**
- **zidovudine - used to treat HIV and AIDS**

When you first start taking Epilim or if you are taking it with other medicines you may notice some drowsiness, if affected you should not drive or operate machinery.

Taking this medicine.

Adults:- The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity should be divided and taken in 2 separate doses e.g. half in the morning and half in the evening.

Children over 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Children under 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is 20mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.

If you have kidney problems your doctor may prescribe a lower dose.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the right time take it as soon as you remember then go on as before.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Whilst taking this medicine.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, loss of appetite, jaundice, swelling of the legs or worsening of your epilepsy. Your doctor may wish to do tests before you start treatment and for the first six months of treatment. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems, **kidney problems** or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may cause tiredness; confusion; hallucinations; change in mood; jerky muscle movements and loss of consciousness. **Rashes, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk.** If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred: if you have lupus, please tell your doctor before taking Epilim.

Do not use this medicine after the expiry date which you will find on the pack.

Epilim tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Date of last revision **September** 1997

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

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APPROVED
23/9/98

EPILIM ENTERIC COATED TABLETS
(Sodium valproate)
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of this medicine is Epilim Enteric Coated tablets.

What is in this medicine?

Each Epilim 200 Enteric Coated tablet contains 200mg Sodium Valproate PhEur.

Each Epilim 500 Enteric Coated tablet contains 500mg Sodium Valproate PhEur.

Each tablet also contains lactose, polyvidone, croscarmellose sodium, microcrystalline cellulose, hydrated silica, polyvinyl acetate phthalate, talc, macrogol 400, citric acid, hypromellose, titanium dioxide (E171), colloidal anhydrous silica, alumina hydrate, sodium alginate, indigo carmine aluminium lake (E132), carmoisine aluminium lake (E122), beeswax, carnauba wax, polysorbate, water and sorbic acid.

Epilim tablets are round lilac coloured tablets and are supplied in cartons of 100 or 112. *(final printed version to include only marketed pack sizes)*

Epilim is an antiepileptic.

The Product Licence/Authorisation holder is:-

UK
Sanofi Winthrop Ltd
One Onslow Street
Guildford
Surrey
GU1 4YS

Ireland
Sanofi Winthrop Ireland Ltd
United Drug House
Belgard Road
Tallaght
Dublin 24

The manufacturer is:-

Sanofi Winthrop Ltd
Edgefield Avenue
Fawdon
Newcastle Upon Tyne
NE3 3TT
UK

What is this medicine for?

Epilim is used to treat epilepsy (fits).

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APPROVED

Before taking this medicine.

Epilim should not be taken by patients with:-

- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria

If you are diabetic Epilim may make urine tests give false results.

Epilim and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

Breast feeding: - very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors.
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin - an antibiotic
- mefloquine - used to prevent malaria
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS

When you first start taking Epilim or if you are taking it with other medicines you may notice some drowsiness, if affected you should not drive or operate machinery.

Some people may have problems with the following ingredients:

- sorbic acid - this is an irritant and may cause dermatitis
- E122 (carmoisine aluminium lake) which is a colouring agent and can cause allergic type reactions including asthma. This reaction is more common in those people who are also allergic to aspirin

Epilim can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, loss of appetite, jaundice, swelling of the legs or worsening of your epilepsy. Your doctor may wish to do tests before you start treatment and for the first six months of treatment. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems, kidney problems or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may cause tiredness; confusion; hallucinations; change in mood; jerky muscle movements and loss of consciousness. Rashes, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred: if you have lupus, please tell your doctor before taking Epilim.

Do not use this medicine after the expiry date which you will find on the pack.

Epilim tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Date of last revision September 1998

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

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Seven Newcastle
Tel: (0044) 191 4917777

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Brand:	L/LET P/F EPILIM EC UK
Category:	LEAFLET PF
Argus Code:	473
Spec No:	30504102
Supersedes:	30504101
Core Spec No:	60100400
Ticket No:	SCP10034
Date:	16.03.01
Issue No:	4
Operator:	KW
Page:	1 of 2
Unwind:	0
Size:	210 x 150 mm
Win/RFL Ref:	0000
Barcode:	N/A
Mag:	N/A
BWR:	N/A

BWR to be assigned by printer.

No. colours and varnish: 1

Black

Material: LAVENDER BOND 60g/m2

Artwork Approval

Reason for Circulation:

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Packaging Development
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Signature:

Marketing
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Date:
Signature:

Pharmacist/Medical Affairs
Approved: Yes ○ No ○ N/A ○
Date:
Signature:

Regulatory Affairs
Approved: Yes ○ No ○
Date:
Signature:

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EPILIM® ENTERIC COATED TABLETS (Sodium Valproate)

PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.
The name of this medicine is Epilim Enteric Coated tablets.

WHAT IS IN THIS MEDICINE?

Each Epilim 200 Enteric Coated tablet contains 200mg Sodium Valproate.
Each Epilim 500 Enteric Coated tablet contains 500mg Sodium Valproate.
Each tablet also contains polyvidone, talc, magnesium stearate, calcium silicate, polyvinyl acetate phthalate, citric acid, hypromellose, macrogol 6000, violet lake, diethyl phthalate, stearic acid, industrial methylated spirits and purified water.
Epilim tablets are round lilac coloured tablets and are supplied in cartons of 100.
Epilim is an antiepileptic.

Product Licence holder:
Sanofi-Synthelabo
PO Box 597
Guildford
Surrey

Manufactured by:
Fawdon Manufacturing Centre
Edgefield Avenue
Fawdon
Newcastle-upon-Tyne
Tyne & Wear
NE3 3TT

WHAT IS THIS MEDICINE FOR?

Epilim is used to treat epilepsy (fits).

BEFORE TAKING THIS MEDICINE?

Epilim should not be taken by patients with:-
- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria (a rare metabolic condition)

If you have lupus (an inflammatory skin disease), please tell your doctor before taking Epilim.
Your doctor may wish to do tests before you start your treatment and for the first six months of your treatment.
If you are diabetic Epilim may make urine tests give false results.
Epilim and Pregnancy
It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1 – 2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.
Breast feeding:- very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.
If taken with some other medicines the effects of Epilim or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:
- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, imipenem and meropenem - antibiotics
- mefloquine - used to prevent malaria

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- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- temozolomide - used to treat cancer

Taking Epilim with chloroquine, which is used to prevent or treat malaria, may make it more likely that you may have seizures. Before travelling you should discuss taking malaria tablets with your doctor or pharmacist.
When you first start taking Epilim or if you are taking it with other medicines you may notice some drowsiness, if affected you should not drive or operate machinery.

TAKING THIS MEDICINE

The tablets should be swallowed whole with a drink of water and not crushed or chewed, usually after meals.
Adults:- The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity should be divided and taken in 2 separate doses e.g. half in the morning and half in the evening.
Children over 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.
Children under 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is 20mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.
If you are taking other medicines to control your epilepsy at the same time as Epilim your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.
If you have kidney problems your doctor may prescribe a lower dose.
If you forget to take a dose at the right time take it as soon as you remember then go on as before.
An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.
Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

WHILST TAKING THIS MEDICINE

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.
Epilim can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your epilepsy or a general feeling of being unwell. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood (which may cause vomiting, unsteady movements and an unawareness of your surroundings); vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems, kidney problems, acne, increased hair growth in women or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may cause tiredness; confusion; hallucinations; seizures; change in mood; jerky muscle movements and loss of consciousness. Rashes, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred.

Do not take this medicine after the month shown on the pack.

Epilim tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Date of revision of leaflet: February 2001.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The British Epilepsy Association (telephone: 0808 800 5050) will also be happy to try and answer any general questions on epilepsy.

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Seven Newcastle
Tel: (0044) 191 4917777

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Brand:	L/LET P/F EPILIM EC UK
Category:	LEAFLET PF
Argus Code:	473
Spec No:	30504102
Supersedes:	30504101
Core Spec No:	60100400
Ticket No:	SCP10034
Date:	16.03.01
Issue No:	4
Operator:	KW
Page:	2 of 2
Unwind:	0
Size:	210 x 150 mm
Win/RFL Ref:	0000
Barcode:	N/A
Mag:	N/A
BWR:	N/A

BWR to be assigned by printer.

No. colours and varnish: 1

Black

Material: LAVENDER BOND 60g/m2

Artwork Approval

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Packaging Development
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Date:
Signature:

Marketing
Approved: Yes ○ No ○ N/A ○
Date:
Signature:

Pharmacist/Medical Affairs
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Date:
Signature:

Regulatory Affairs
Approved: Yes ○ No ○
Date:
Signature:

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30514201

EPILIM ENTERIC COATED TABLETS (Sodium Valproate)

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- It is essential that you follow your doctor's advice.
- If you are helping someone else to take Epilim Enteric Coated tablets, read this leaflet carefully before you give them the first dose.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

Each Epilim 200 Enteric Coated tablet contains 200mg Sodium Valproate.
Each Epilim 500 Enteric Coated tablet contains 500mg Sodium Valproate.
They also contain povidone, talc, magnesium stearate, calcium silicate, polyvinyl acetate phthalate, citric acid, hypromellose, macrogol 8000, violet lake solids containing titanium dioxide (E171, amaranth lake (E123, indigo carmine lake (E132), hydroxypropyl cellulose, diethyl phthalate and stearic acid.
Product Licence holder: Sanofi-Synthelabo, PO Box 587, Guildford, Surrey
Manufactured by: Fawdon Manufacturing Centre, Edgefield Avenue, Fawdon, Newcastle-upon-Tyne, Tyne & Wear, NE3 3TT.

1. WHAT ARE EPILIM ENTERIC COATED TABLETS AND WHAT ARE THEY USED FOR?

Epilim Enteric Coated tablet are an antiepileptic. That is it is used to treat epilepsy (fits).
Epilim Enteric Coated tablets are round, lilac coloured tablets and are supplied in cartons of 100.

2. BEFORE YOU TAKE/USE EPILIM ENTERIC COATED TABLETS

Do not take/use Epilim Enteric Coated tablets if you have:
- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria (a rare metabolic condition)

Tell your doctor before starting Epilim Enteric Coated tablets if you:
- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose

You should talk to your doctor or pharmacist even if you no longer have these conditions, but have had them in the past.
Your doctor may wish to do tests before you start and during the first six months of treatment.

Taking/having Epilim Enteric Coated tablets with food and drink
The tablets should be swallowed immediately. They should be swallowed whole, usually after meals, with a drink of water and not crushed or chewed.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. It is essential that you discuss your epilepsy treatment with your doctor well before you become pregnant. If at any time you suspect that you might already be pregnant you must tell your doctor immediately.
Women who take Epilim during the first month of pregnancy to control their epilepsy have a small risk (1-2%) of having a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida.
There is also an increased risk of other birth defects. These can usually be detected in the first part of the pregnancy using routine antenatal screening blood tests and ultrasound scans. Rarely there may also be bleeding problems in the new born if the mother has taken Epilim during pregnancy.
Infants born to mothers who took Epilim during pregnancy may develop less quickly than normal. This may also be because of the mother's epilepsy but the exact cause is not known.
It is important not to stop your Epilim suddenly as this is likely to result in you having fits which may harm both you and your baby.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

Driving and using machines
When you first start taking Epilim, or if you are taking it with other medicines, you may notice some drowsiness. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Epilim Enteric Coated tablets
Epilim Enteric Coated tablets contain amaranth lake and indigo carmine lake, which may cause allergic reactions in some people.

Taking/using other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine – even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.
If taken with some other medicines the effects of Epilim Enteric Coated tablets or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:
- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin

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Brand:	LLET RFED EPILIM UK
Category:	LEAFLET
Argus Code:	252
Spec No:	30514201
Supersedes:	N/A
Core Spec No:	60101600
Ticket No:	SCP26400
Date:	24.11.03
Issue No:	5
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Page:	1 of 2
Unwind:	FRONT 5
Size:	211.7 x 148mm
Win/RFL Ref:	RFL026
Barcode:	N/A
Mag:	N/A
SWR:	N/A
SWR to be assigned by printer.	

No. colours and varnish: 1

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Artwork Approval

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Packaging Development
Approved: Yes○ No○
Date:
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Marketing
Approved: Yes○ No○ N/A○
Date:
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Pharmacist/Medical Affairs
Approved: Yes○ No○ N/A○
Date:
Signature:

Regulatory Affairs
Approved: Yes○ No○
Date:
Signature:

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60101600

* Material: Lavender Bond 60gsm *

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- erythromycin, imipenem and meropenem - antibiotics
- mefloquine and chloroquine - used to prevent and treat malaria - may increase the likelihood of a fit. Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- temozolomide - used to treat cancer

The effects of Sodium Valproate may also be changed by medicines taken some time ago, or it may change the effects of medicines you may take in the future.

3. HOW TO TAKE/USE EPILIM ENTERIC COATED TABLETS

They should be swallowed immediately. They should be swallowed whole, usually after meals with a drink of water and not crushed or chewed.

Adults:- The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity should be divided and taken in 2 separate doses e.g. half in the morning and half in the evening.

Children over 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Children under 20kg:- The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is 20mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

When treatment is first started you may be prescribed a lower dose. This is because some patients react less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim Enteric Coated tablets your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.

If you have kidney disease your doctor may prescribe a lower dose.

If you take/use more Epilim Enteric Coated tablets than you should:

An overdose of this medicine may be dangerous. If you think you or someone else may have taken/used more Epilim Enteric Coated tablets than you should, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

If you forget to take/have Epilim Enteric Coated tablets:

If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. However, you must take care not to take two doses at the same time.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Epilim Enteric Coated tablets can have side-effects. Epilim can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment, and particularly if it includes repeated vomiting and extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs or worsening of your epilepsy or a general feeling of being unwell.

Particular care is needed in the case of children under 3 or those with other nervous system disease.

Whilst taking your tablets your appetite may be increased and you must take care to avoid weight gain.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; diarrhoea; changes in the amount of ammonia in the blood (which may cause vomiting, unsteady movements and an unawareness of your surroundings); vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; weakness or problems with balance. Rarely it may cause tiredness; confusion; suicidal; change in mood, jerky muscle movements and loss of consciousness. Epilim may cause some tests to give false results.

Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before.

Rashes may occur, which can sometimes be severe and appear in patches, sometimes with broken skin. These occur rarely, but patients who are also taking lamotrigine may be more at risk. In exceptional cases blisters, which may burst followed by shedding of the skin, may occur. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also, immune disorders have occurred rarely.

Very rarely it may also cause a change in women's periods or lead to the stoppage of periods, hearing problems, kidney problems, acne, increased hair growth or worse or increased breast growth in men. Very rarely symptoms of Parkinson disease (shaking) or dementia (memory loss) can occur but these effects are reversible.

If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING EPILIM ENTERIC COATED TABLETS

Keep your medicine in a safe place where children cannot reach it.

Epilim Enteric Coated tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Do not take this medicine after the month shown on the pack.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

The British Epilepsy Association (telephone: 0808 800 5050) will also be happy to try and answer any general questions on epilepsy.

Date of revision of leaflet: November 2003.

30514201

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seven

Seven Newcastle
Tel: (0044) 191 4917777

sanofi~synthelabo

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Category:	LEAFLET
Argus Code:	252
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Supersedes:	N/A
Core Spec No:	60101600
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EPILIM® ENTERIC COATED TABLETS (Sodium Valproate)

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- **Keep this leaflet. You may need to read it again.**
- **It is essential that you follow your doctor's advice.**
- **If you are helping someone else to take Epilim Enteric Coated Tablets, read this leaflet carefully before you give them the first dose.**
- **If you have further questions, please ask your doctor or pharmacist.**
- **This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.**

In this leaflet:

Each Epilim 200 Enteric Coated tablet contains 200mg Sodium Valproate.
Each Epilim 500 Enteric Coated tablet contains 500mg Sodium Valproate.
They also contain povidone, talc, magnesium stearate, calcium silicate, polyvinyl acetate phthalate, citric acid, hypromellose, macrogol 6000, violet lake solids containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132), hydroxypropyl cellulose, diethyl phthalate and stearic acid.
Product Licence Holder: Sanofi-Synthelabo, PO Box 597, Guildford, Surrey
Manufactured by: Fawdon Manufacturing Centre, Edgefield Avenue, Fawdon, Newcastle-upon-Tyne, Tyne & Wear, NE3 3TT.

1. WHAT ARE EPILIM ENTERIC COATED TABLETS AND WHAT ARE THEY USED FOR?

Epilim Enteric Coated tablets are an antiepileptic, which is used to treat epilepsy (fits).
Epilim Enteric Coated tablets are round, lilac coloured tablets and are supplied in cartons of 100 tablets.

2. BEFORE YOU TAKE EPILIM ENTERIC COATED TABLETS

Do not take Epilim Enteric Coated tablets if you have:
- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria (a rare metabolic condition)

Tell your doctor before starting Epilim Enteric Coated tablets if you:
- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose

You should talk to your doctor or pharmacist even if you no longer have these conditions, but have had them in the past.
Your doctor may wish to do blood tests before you start taking these tablets and during the first six months of treatment.

Taking/using Epilim Enteric Coated tablets with food and drink
The tablets should be swallowed immediately. They should be swallowed whole, usually after meals, with a drink of water and not crushed or chewed. Do not stop taking Epilim or change the number of tablets you are taking without first discussing this with your doctor, as this may lead to a recurrence of your symptoms.

When special care with Epilim Enteric Coated Tablets is needed
- if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe upper stomach pains, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your condition or a general feeling of being unwell, YOU SHOULD TELL YOUR DOCTOR IMMEDIATELY. Epilim can affect the liver (and rarely the pancreas) in a very small number of patients.

If you have any of the following speak to your doctor before starting your tablets:
- systemic lupus erythematosus (a rare disease),
- from any metabolic disorders, particularly hereditary enzyme deficiency disorders such as a urea cycle disorder because of a risk of increased ammonia level in the blood,
- impaired kidney function. Your doctor may want to monitor your blood valproate level or adapt your dose,
- an increased appetite and are putting on weight.

Pregnancy

Information for Women who could become Pregnant

Before you start treatment, your doctor should discuss with you the problems that may arise if Epilim is used in pregnancy.

Unplanned pregnancy is not desirable in women receiving Epilim. You should use an effective method of contraception and consult your doctor before planning pregnancy. Epilim has no effect on how well your oral contraceptive pill works.
It is known that women receiving Epilim during pregnancy have a higher risk than other women of giving birth to a child with an abnormality. The likelihood of abnormalities is increased if you are also taking antiepileptic medicines at the same time. These effects include;
- head and facial deformities including cleft palate – a gap or depression in the lip
- deformities of the bones including hip dislocation
- malformation of the limbs
- deformities of the urogenital tract including defects in the wall of the male urethra or vagina leading to an additional opening
- cardiovascular malformations, including heart defects
- defects in the lining of nerve tubes, such as holes or protrusions
- spina bifida

Women who take Epilim during pregnancy may be more likely to have a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. These can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.
Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support.
There may also be blood clotting problems (such as blood not clotting or not clotting very well) in the new born babies of mothers who have taken Epilim during pregnancy. This may appear as bruising or a delay in the stoppage of bleeds.
It is important not to stop your Epilim suddenly as this is likely to result in a relapse of your symptoms.

Information for Women who are planning to get Pregnant

If you become pregnant or think you may be pregnant whilst taking Epilim, you must tell your doctor immediately. Consult your doctor before planning pregnancy in order to receive appropriate counselling and to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy. It is essential that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

Driving and using machines
When you first start taking Epilim, or if you are taking it with other medicines, such as other antiepileptic drugs or benzodiazepines, you may notice some drowsiness. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Epilim Enteric Coated tablets
Epilim Enteric Coated tablets contain amaranth lake and indigo carmine lake, which may cause allergic reactions in some people.

Taking/using other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine – even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.
If taken with some other medicines the effects of Epilim Enteric Coated tablets or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:
- colestyramine - used to treat high blood lipid (fat) levels
- antipsychotic agents (used to treat psychological disorders) - Epilim may increase the effects of these drugs.
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbital, lamotrigine, primidone, felbamate
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, carbapenem such as imipenem, panipenem and meropenem antibiotics
- mefloquine and chloroquine - use to prevent and treat malaria - may increase the likelihood of a fit. Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- temozolomide - used to treat cancer

When used in combination with olanzepine the following effects may occur; neutropenia – a blood disorder leading to a reduced chance of fighting infection, tremor, dry mouth, increased appetite and weight gain, problems with speech or sleepiness or extreme tiredness

3. HOW TO TAKE EPILIM ENTERIC COATED TABLETS

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim Enteric Coated Tablets.

They should be swallowed immediately. They should be swallowed whole, usually after meals with a drink of water and not crushed or chewed.

Adults: The usual dose of Epilim is between 1000mg and 2000mg per day but may be increased to 2500mg per day.
This quantity should be divided and taken in 2 separate doses e.g. half in the morning and half in the evening.

Children over 20kg: The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day.
This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Children under 20kg: The usual dose of Epilim is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is 20mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed. If you are taking other medicines to control your epilepsy at the same time as Epilim Enteric Coated tablets your doctor may increase the dose of Epilim by 5 to 10mg for each kg of body weight per day.

If you have kidney disease your doctor may prescribe a lower dose.

If you take more Epilim Enteric Coated tablets than you should:
An overdose of this medicine may be dangerous. If you think you may have taken more Epilim Enteric Coated tablets than you should or someone else has taken some, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

If you forget to take Epilim Enteric Coated tablets:
If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. However, you must not take two doses at the same time.
Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better, as this may lead to an immediate relapse. If you stop them your condition may get worse.
Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.
If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Epilim Enteric Coated tablets can have side-effects. Rarely they are serious, most of the time they are not. Usually they are reversible. You may need medical treatment if you get some of the side effects.

Tell your doctor IMMEDIATELY if you notice any of the following serious side effects. You may need urgent medical attention.

- repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe upper stomach pain, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your epilepsy or a general feeling of being unwell.

Epilim Enteric Coated Tablets can affect the liver (and rarely the pancreas) in a very small number of patients.
You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment.
If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets.

- bizarre behaviour, an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. This can be associated with more frequent or severe fits, loss of drive, particularly if phenobarbital is taken at the same time or if the Epilim dose has been suddenly increased.
- blood clotting problems
- spontaneous bruising or bleeding
- blisters with skin detachment.

If you experience any of the effects covered in this section, you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform you doctor or pharmacist.

- nausea or stomach ache, vomiting, diarrhoea, especially when starting the treatment
- shakiness (tremor), drowsiness, unsteadiness when walking
- tiredness, confusion, hallucinations, change in mood
- jerky muscle movements
- loss of consciousness
- skin reactions such as rashes, occur rarely but patients who are also taking lamotrigine may be more at risk
- nausea (usually relieved by taking tablets with or after food)
- changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching
- any loss of hair is usually temporary but when it grows back it may be more curly than before
- changes in women's periods
- hearing problems
- acne
- increased hair growth in women
- increased breast growth in men
- allergic reactions
- swelling of the feet and legs (oedema)
- weight gain as your appetite may be increased
- kidney problems, bedwetting or increased need to pass urine
- immune disorders.

These effects usually reverse on stopping the Epilim Enteric Coated Tablets.
Epilim Enteric Coated Tablets may cause a decrease in blood sodium which can result in tiredness, weakness, dizziness, feeling faint/fainting, nausea, vomiting and muscle cramps. Less commonly there may be bloating, swelling, tightness of the hands and feet, confusion and seizures. Sometimes it can cause changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily, severe stomach pains, shakiness or problems with balance.

5. STORING EPILIM ENTERIC COATED TABLETS

Keep your medicine in a safe place where children cannot see or reach it. Epilim Enteric Coated tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Do not take this medicine after the month shown on the pack.
This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.
Date of revision of leaflet: June 2005
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There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at;

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400. Website:www.epilepsynse.org.uk

seven

Seven Newcastle
Tel: (0044) 191 4917777

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Brand:	LLET RFED EPILIM UK
Category	LEAFLET
Argus Code:	519
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Pharmacist/Medical Affairs
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Regulatory Affairs
Approved: Yes○ No○
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- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blisters with the skin flaking away

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food
- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, bedwetting or increased need to pass urine

Blood tests
Epilim EC can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Epilim EC

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Epilim EC contains
- Each 200mg enteric coated tablet contains 200mg of the active substance, sodium valproate
- Each 500mg enteric coated tablet contains 500mg of the active substance, sodium valproate
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid anhydrous (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

What Epilim EC looks like and contents of the pack
Epilim EC tablets are round and lilac coloured. The tablets are supplied in blister packs of 100

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi-aventis
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Guildford
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GU1 4YS
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Tel: 01483 505515
Fax: 01483 535432
email: uk-medicalinformation@sanofi-aventis.com

Manufacturer
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Edgefield Avenue
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UK

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 05/2010

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400. Website: www.epilepsynse.org.uk

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Epilim® 200mg and 500mg Enteric Coated Tablets

sodium valproate

sanofi aventis

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Epilim EC is and what it is used for

What Epilim EC is
The name of your medicine is Epilim 200mg and 500mg Enteric Coated Tablets (called Epilim EC in this leaflet). "Enteric coated" means that the tablet has a protective coating that allows it to reach the intestines (gut) without being dissolved in the stomach first. This helps stop it from causing a stomach upset.

What Epilim EC contains
Epilim EC contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim EC is used for
Epilim EC is used to treat epilepsy (fits) in adults and children.

2. Before you take Epilim EC

Do not take Epilim EC and tell your doctor if:
× You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim EC (see Section 6: Further information)
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
× You have liver problems or you or your family have a history of liver problems
× You have a rare illness called porphyria
Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim EC.

Take special care with Epilim EC
A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking this medicine if:
▲ You have diabetes. This medicine may affect the results of urine tests
▲ You have kidney problems. Your doctor may give you a lower dose
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body.
▲ You have an illness called "systemic lupus erythematosus (SLE)" - a disease of the immune system which affects skin, bones, joints and internal organs
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim EC.

Weight gain
Taking Epilim EC may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim EC and during your treatment.

Taking Epilim EC with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim EC can affect the way some other medicines work. Also some medicines can affect the way Epilim EC works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim EC:
- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, "Patients taking other medicines for 'fits'". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate

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Epilim EC may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin)
- Zidovudine used to treat HIV infection
- Temozolomide used to treat cancer
- Medicines for depression
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

The following medicines can affect the way Epilim EC works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine used for stomach ulcers
- Some medicines used for infections (antibiotics) such as imipenem, meropenem, rifampicin and erythromycin
- Colestyramine used to lower blood fat (cholesterol) levels

Pregnancy and breast-feeding

Women who could become pregnant

Before you start taking Epilim EC, your doctor should discuss with you the possible problems when it is taken in pregnancy.
- Unplanned pregnancy is not desirable in women taking Epilim EC
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.** Epilim EC has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy and epilepsy with your doctor and, if you have one, your epilepsy specialist. This is to make sure that you and your doctor agree that you should have Epilim if you become pregnant.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:
- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tubes from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations, including heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina bifida'

Women who take Epilim EC during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim EC may have babies with blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.

Some babies born to mothers who took Epilim EC during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim EC if you want to become pregnant. Do not stop taking Epilim EC suddenly, as it is likely that your fits will come back.

Women who are planning to get Pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim EC, you must tell your doctor straight away.
- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding

Very little Epilim EC gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

You may feel sleepy when taking Epilim EC. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim EC

Always take Epilim EC exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Your doctor will decide how much Epilim EC to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- **Do not** crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine
- The dose is normally split and given half in the morning and half in the evening

How much to take

Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day
- Depending on the child's condition your child's doctor may decide to increase the dose

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim EC. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of Epilim EC by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim EC than you should

If you take more Epilim EC than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim EC

If you forget to take a dose, take it as soon as you remember. However, if it nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epilim EC

Keep taking until your doctor tells you to stop. Do not stop taking Epilim EC just because you feel better. If you stop your fits may come back.

Tests

Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim EC can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly.
If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim EC.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim EC can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim EC. It includes feeling and being sick many times, being very tired, sleepy and weak, stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling (especially of the legs and feet but may include other parts of the body), worsening of your fits or a general feeling of being unwell
  Your doctor may tell you to stop taking Epilim EC immediately if you have these symptoms
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia)
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma)

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim EC starting dose is high or has been suddenly increased

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Supersedes:	30514204
Core Spec No:	60101300
Ticket No:	272470
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Issue No:	3
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Page:	2 of 2
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- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blisters with the skin flaking away

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food
- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, bedwetting or increased need to pass urine

Blood tests
Epilim EC can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male Fertility
Taking Epilim EC can be a contributing factor in male infertility.

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Epilim EC

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Epilim EC contains
- Each 200mg enteric coated tablet contains 200mg of the active substance, sodium valproate
- Each 500mg enteric coated tablet contains 500mg of the active substance, sodium valproate
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid anhydrous (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

What Epilim EC looks like and contents of the pack
Epilim EC tablets are round and lilac coloured. The tablets are supplied in blister packs of 100

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 01483 505515
Fax: 01483 535432
email: uk-medicalinformation@sanofi-aventis.com

Manufacturer
Fawdon Manufacturing Centre,
Edgefield Avenue
Fawdon
Newcastle-upon-Tyne
Tyne & Wear
NE3 3TT
UK

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 06/2011

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400. Website: www.epilepsynse.org.uk

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Epilim® 200mg and 500mg Enteric Coated Tablets

sodium valproate

sanofi aventis

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Epilim EC is and what it is used for

What Epilim EC is
The name of your medicine is Epilim 200mg and 500mg Enteric Coated Tablets (called Epilim EC in this leaflet). "Enteric coated" means that the tablet has a protective coating that allows it to reach the intestines (gut) without being dissolved in the stomach first. This helps stop it from causing a stomach upset.

What Epilim EC contains
Epilim EC contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim EC is used for
Epilim EC is used to treat epilepsy (fits) in adults and children.

2. Before you take Epilim EC

Do not take Epilim EC and tell your doctor if:
× You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim EC (see Section 6: Further information)
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
× You have liver problems or you or your family have a history of liver problems
× You have a rare illness called porphyria
Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim EC.

Take special care with Epilim EC
A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking this medicine if:
▲ You have diabetes. This medicine may affect the results of urine tests
▲ You have kidney problems. Your doctor may give you a lower dose
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body.
▲ You have an illness called "systemic lupus erythematosus (SLE)" - a disease of the immune system which affects skin, bones, joints and internal organs
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim EC.

Weight gain
Taking Epilim EC may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim EC and during your treatment.

Taking Epilim EC with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim EC can affect the way some other medicines work. Also some medicines can affect the way Epilim EC works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim EC:
- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, "Patients taking other medicines for 'fits'". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate

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Epilim EC may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin)
- Zidovudine used to treat HIV infection
- Temozolomide used to treat cancer
- Medicines for depression
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

The following medicines can affect the way Epilim EC works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine used for stomach ulcers
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim EC and carbapenems should be avoided because it may decrease the effect of your medicine.
- Colestyramine used to lower blood fat (cholesterol) levels

Taking Epilim EC with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding

Women who could become pregnant

You should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor.

Before you start taking Epilim EC, your doctor should discuss with you the possible problems when it is taken in pregnancy.
- Unplanned pregnancy is not desirable in women taking Epilim EC
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.** Epilim EC has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy and epilepsy with your doctor and, if you have one, your epilepsy specialist. This is to make sure that you and your doctor agree that you should have Epilim if you become pregnant.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:
- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tubes from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations, including heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina bifida'

Women who take Epilim EC during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim EC may have babies with:
- blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar)

Some babies born to mothers who took Epilim EC during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim EC if you want to become pregnant. Do not stop taking Epilim EC suddenly, as it is likely that your fits will come back.

Women who are planning to get Pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim EC, you must tell your doctor straight away.
- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding

Very little Epilim EC gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

You may feel sleepy when taking Epilim EC. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim EC

Always take Epilim EC exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Your doctor will decide how much Epilim EC to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- **Do not** crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine
- The dose is normally split and given half in the morning and half in the evening

How much to take

Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day
- Depending on the child's condition your child's doctor may decide to increase the dose

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim EC. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of Epilim EC by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim EC than you should

If you take more Epilim EC than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim EC

If you forget to take a dose, take it as soon as you remember. However, if it nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epilim EC

Keep taking until your doctor tells you to stop. Do not stop taking Epilim EC just because you feel better. If you stop your fits may come back.

Tests

Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim EC can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly.

If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim EC.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim EC can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim EC. It includes feeling and being sick many times, being very tired, sleepy and weak, stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling (especially of the legs and feet but may include other parts of the body), worsening of your fits or a general feeling of being unwell Your doctor may tell you to stop taking Epilim EC immediately if you have these symptoms
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia)
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma)

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim EC starting dose is high or has been suddenly increased

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- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blisters with the skin flaking away
- Rapid, uncontrollable movement of the eyes

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food
- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, bedwetting or increased need to pass urine
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Blood tests
Epilim can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male Fertility
Taking Epilim can be a contributing factor in male infertility.

Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Epilim

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Further information

What Epilim contains
- Each 200mg gastro-resistant tablet contains 200mg of the active substance, sodium valproate
- Each 500mg gastro-resistant tablet contains 500mg of the active substance, sodium valproate
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid anhydrous (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), violet lake solids (containing titanium dioxide (E171), amaranth lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463))

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Epilim tablets are round and lilac coloured. The tablets are supplied in blister packs of 100

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This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in November 2012

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400. Website: www.epilepsynse.org.uk

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Epilim® 200mg and 500mg Gastro-resistant Tablets

sodium valproate

SANOFI

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Epilim is and what it is used for

What Epilim is
The name of your medicine is Epilim 200mg and 500mg Gastro-resistant Tablets (called Epilim in this leaflet). Epilim 200mg and 500mg Gastro-resistant Tablets are "enteric coated" this means that the tablets have a protective coating that allows it to reach the intestines (gut) without being dissolved in the stomach first. This helps stop it from causing a stomach upset.

What Epilim contains
Epilim contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim is used for
Epilim is used to treat epilepsy (fits) in adults and children.

2. Before you take Epilim

Do not take Epilim and tell your doctor if:
× You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim (see Section 6: Further information)
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
× You have liver problems or you or your family have a history of liver problems
× You have a rare illness called porphyria
Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim.

Take special care with Epilim
A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking this medicine if:
▲ You have diabetes. This medicine may affect the results of urine tests
▲ You have kidney problems. Your doctor may give you a lower dose
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body.
▲ You have an illness called "systemic lupus erythematosus (SLE)" - a disease of the immune system which affects skin, bones, joints and internal organs
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim.

Weight gain
Taking Epilim may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim and during your treatment.

Taking Epilim with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim can affect the way some other medicines work. Also some medicines can affect the way Epilim works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim:
- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, "Patients taking other medicines for 'fits'". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate

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Epilim may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin)
- Zidovudine used to treat HIV infection
- Temozolomide used to treat cancer
- Medicines for depression
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

The following medicines can affect the way Epilim works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine used for stomach ulcers
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim and carbapenems should be avoided because it may decrease the effect of your medicine.
- Colestyramine used to lower blood fat (cholesterol) levels

Taking Epilim with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding

Women who could become pregnant

You should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor.

Before you start taking Epilim, your doctor should discuss with you the possible problems when it is taken in pregnancy.
- Unplanned pregnancy is not desirable in women taking Epilim
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.** Epilim has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy and epilepsy with your doctor and, if you have one, your epilepsy specialist. This is to make sure that you and your doctor agree that you should have Epilim if you become pregnant.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:
- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tubes from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations, including heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina bifida'
- Malformations of the urethra

Women who take Epilim during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim may have babies with:
- blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar)
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).

Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim if you want to become pregnant. Do not stop taking Epilim suddenly, as it is likely that your fits will come back.

Women who are planning to get Pregnant
If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim, you must tell your doctor straight away.
- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding
Very little Epilim gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
You may feel sleepy when taking Epilim. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim

Always take Epilim exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Your doctor will decide how much Epilim to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- **Do not** crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine
- The dose is normally split and given half in the morning and half in the evening

How much to take

Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day
- Depending on the child's condition your child's doctor may decide to increase the dose

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of Epilim by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim than you should
If you take more Epilim than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim
If you forget to take a dose, take it as soon as you remember. However, if it nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epilim
Keep taking until your doctor tells you to stop. Do not stop taking Epilim just because you feel better. If you stop your fits may come back.

Tests
Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly.
If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- You have an allergic reaction. The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim. It includes feeling and being sick many times, being very tired, sleepy and weak, stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling (especially of the legs and feet but may include other parts of the body), worsening of your fits or a general feeling of being unwell
  Your doctor may tell you to stop taking Epilim immediately if you have these symptoms
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma)
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim starting dose is high or has been suddenly increased

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- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, bedwetting or increased need to pass urine
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Blood tests
Epilim can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male Fertility
Taking Epilim can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side eff ects not listed in this leaflet.

United Kingdom
You can also report side effects directly via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard

Malta
ADR Reporting, The Medicines Authority, Post-Licensing Directorate, 203 Level 3, Rue D'Argens,
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

By reporting side effects you can help provide more information on the safety of this medicine.

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5. How to store Epilim

Keep out of the sight and reach of children.

Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the
last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What Epilim contain
- Each 200mg gastro-resistant tablet contains 200mg of the active substance, sodium valproate
- Each 500mg gastro-resistant tablet contains 500mg of the active substance, sodium valproate
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid monohydrate (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hyfroxypropyl cellulose (E463)

What Epilim looks like and contents of the pack
Epilim tablets are round and lilac coloured. The tablets are supplied in blister packs of 100

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis S.A,
Carretera C-35 (La Batlloria-Hostalric), Km 63.09
17404 Riells i Viabrea (Girona)

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in February 2015
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There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be
contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website:
www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400.
Website:www.epilepsynse.org.uk

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Epilim® 200mg and 500mg Gastro-resistant Tablets

sodium valproate

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Is this leaflet hard to see or read? Phone 0845 372 7101 for help

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects

WARNING
Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.
Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epilim is and what it is used for

What Epilim is
The name of your medicine is Epilim 200mg or 500mg Gastro-resistent Tablets (called Epilim in this leaflet). Epilim 200mg or 500mg Gastro-resistant Tablets are "enteric coated" this means that the tablets have a protective coating that allows it to reach the intestines (gut) without being dissolved in the stomach first. This helps stop it from causing a stomach upset.

What Epilim contains
Epilim contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim is used for
Epilim is used to treat epilepsy (fits) in adults and children.

2. What you need to know before you take Epilim

Do not take Epilim and tell your doctor if:
- x You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim (see Section 6: Contents of the pack and other information)
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- x You have liver problems or you or your family have a history of liver problems
- x You have a rare illness called porphyria
- x If you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim.

Warnings and precautions
A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor or pharmacist before taking Epilim if:
- ▲ You have diabetes. This medicine may affect the results of urine tests.
- ▲ You have kidney problems. Your doctor may give you a lower dose
- ▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain
- ▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body
- ▲ You have an illness called 'systemic lupus erythematosus (SLE)' - a disease of the immune system which affects skin, bones, joints and internal organs
- ▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim.

Weight gain
Taking Epilim may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim and during your treatment.

Other medicines and Epilim
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim can affect the way some other medicines work. Also some medicines can affect the way Epilim works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim:
- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, "Patients taking other medicines for 'fits'". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate

Epilim may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin)
- Zidovudine - used for HIV infection
- Temozolomide used to treat cancer
- Medicines for depression
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

The following medicines can affect the way Epilim works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine - used for stomach ulcers
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim and carbapenems should be avoided because it may decrease the effect of your medicine
- Colestyramine used to lower blood fat (cholesterol) levels

Taking Epilim with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy is controlled and the risks to your baby are reduced
- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.

Breast-feeding

Very little Epilim gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel sleepy when taking Epilim. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim

Always take Epilim exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Epilim treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine

- Your doctor will decide how much Epilim to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- **Do not** crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine

- The dose is normally split and given half in the morning and half in the evening.

How much to take

Adults (including the elderly)

- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms

- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness

Children under 20 kilograms

- The usual dose is 20mg for each kilogram of body weight each day
- Depending on the child's condition your child's doctor may decide to increase this dose

Patients with kidney problems

- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)

- You or your child may be taking other medicines for epilepsy at the same time as Epilim. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of Epilim by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim than you should

If you take more Epilim than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.
The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim

If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epilim

Keep taking until your doctor tells you to stop. Do not stop taking Epilim just because you feel better. If you stop your fits may come back.

Tests

Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- You have an allergic reaction. The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim. It includes feeling and being sick many times, being very tired, sleepy and weak, stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling (especially of the legs and feet but may include other parts of the body), worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Epilim immediately if you have these symptoms
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma)
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)

Tell your doctor as soon as possible if you have any of the following side effects:

- Changes in behaviour including being very alert, and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim starting dose is high or has been suddenly increased
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blisters with the skin flaking away
- Rapid, uncontrollable movement of the eyes

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:

- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food

- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion).

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyperactive and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim starting dose is high or has been suddenly increased.
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert.
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements.
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits.
- Blisters with the skin flaking away.
- Rapid, uncontrollable movement of the eyes.
- An increase in the number and severity of convulsions.

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick (nausea), being sick (vomiting), stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food.
- Swelling of gums or sore mouth
- Fainting
- Hearing loss
- Nail and nail bed disorders
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine.
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before.
- Hair disorders (changes in texture, colour or growth)
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain – as your appetite may be increased
- Kidney disease
- Kidney problems, bedwetting or increased need to pass urine
- Blood in the urine
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)
- Obesity

Bone disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Blood tests
Epilim can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male fertility
Taking Epilim can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

United Kingdom
You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta
You can also report side effects directly via ADR Reporting: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epilim

Keep out of the sight and reach of children.
Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.
Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips.
Store in a dry place below 30°C.
Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What Epilim Gastro-resistant Tablets contain
- Each 200mg gastro-resistant tablet contains 200mg of the active substance, sodium valproate.
- Each 500mg gastro-resistant tablet contains 500mg of the active substance, sodium valproate.
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid monohydrate (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463).

What Epilim Gastro-resistant Tablets look like and contents of the pack
Epilim tablets are round and lilac coloured. The tablets are supplied in blister packs of 100.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis S.A,
Carretera C-35 (La Batlloria-Hostalric), Km 63.09
17404 Riells i Viabrea (Girona), Spain

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in April 2018

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050
Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400
Website: www.epilepsynse.org.uk

170 x 315 mm
68893-6497414

Avance bobina

PACKAGE LEAFLET: INFORMATION FOR THE USER

Epilim® 200mg and 500mg Gastro-resistant Tablets

sodium valproate

SANOFI

Is this leaflet hard to see or read? Phone 0845 372 7101 for help.

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING

Epilim, sodium valproate, can seriously harm an unborn baby when taken during pregnancy. If you are a female able to have a baby you must use an effective method of birth control (contraception) without interruption during your entire treatment with Epilim. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.

Do not stop taking Epilim unless your doctor tells you to as your condition may become worse.

If you are a parent or caregiver of a female child treated with Epilim, you must also read section 2 of this leaflet carefully and contact your child's doctor once they experience their first period.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epilim is and what it is used for

What Epilim is
The name of your medicine is Epilim 200mg or 500mg Gastro-resistant Tablets (called Epilim in this leaflet). Epilim 200mg or 500mg Gastro-resistant Tablets are "enteric coated" this means that the tablets have a protective coating that allows them to reach the intestines (gut) without being dissolved in the stomach first. This helps stop them from causing a stomach upset.

What Epilim contains
Epilim contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim is used for
Epilim is used to treat epilepsy (fits) in adults and children.

2. What you need to know before you take Epilim

Do not take Epilim and tell your doctor if:
X You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim (see Section 6: Contents of the pack and other information). Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
X You have liver problems or you or your family have a history of liver problems.
X You have a rare illness called porphyria.
X You have a known metabolic disorder, i.e. a urea cycle disorder.
X You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
X You are pregnant, unless nothing else works for you (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).

If you are a woman able to have a baby you must not take Epilim unless you use an effective method of birth control (contraception) at all times during your treatment with Epilim. Do not stop taking Epilim or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim.

Warnings and precautions
- A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking Epilim if:
▲ You have diabetes. This medicine may affect the results of urine tests.
▲ You have a carnitine palmitoyltransferase type II deficiency.
▲ You have kidney problems. Your doctor may give you a lower dose.
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body.
▲ You have an illness called 'systemic lupus erythematosus (SLE)' – a disease of the immune system which affects skin, bones, joints and internal organs.
▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim.

Weight gain
Taking Epilim may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim and during your treatment.

Other medicines and Epilim
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim can affect the way some other medicines work. Also some medicines can affect the way Epilim works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim:
- Some medicines used for pain and inflammation (salicylates) such as aspirin.
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, 'Patients taking other medicines for fits'. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate.

Epilim may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin).
- Zidovudine – used for HIV infection.
- Temozolomide used to treat cancer.
- Medicines for depression.
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.
- Nimodipine.
- Propofol – used for anaesthesia.

The following medicines can affect the way Epilim works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine.
- Cimetidine – used for stomach ulcers.
- Protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim and carbapenems should be avoided because it may decrease the effect of your medicine.
- Cholestyramine used to lower blood fat (cholesterol) levels.

Taking Epilim with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women
- You must not use Epilim if you are pregnant, unless nothing else works for you.
- If you are a woman able to have a baby, you must not take Epilim unless you use an effective method of birth control (contraception) during your entire treatment with Epilim.
- Do not stop taking Epilim or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy
- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:
- **I AM STARTING TREATMENT WITH EPILIM**
- **I AM TAKING EPILIM AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING EPILIM AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING EPILIM**

I AM STARTING TREATMENT WITH EPILIM
If this is the first time you have been prescribed Epilim your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with Epilim. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- Pregnancy must be excluded before start of treatment with Epilim with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Epilim.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING EPILIM AND NOT PLANNING TO HAVE A BABY
If you are continuing treatment with Epilim but you are not planning to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Epilim. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with Epilim.
- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING EPILIM AND PLANNING TO HAVE A BABY
If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking Epilim or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development, which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of Epilim, switch you to another medicine, or stop treatment with Epilim a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking Epilim unless your doctor tells you to.
- Do not stop using your birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine or stop treatment with Epilim a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING EPILIM
Do not stop taking Epilim unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of epilepsy so that alternative treatment options can be evaluated.

In the exceptional circumstances when Epilim is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking Epilim unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Epilim during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the Patient Guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
Very little Epilim gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may feel sleepy when taking Epilim. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim

Always take Epilim exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Epilim treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine
- Your doctor will decide how much Epilim to give you or your child depending on your or your child's body weight.
- Take this medicine by mouth.
- **Do not** crush or chew the tablets.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor.

How to take this medicine
- The dose is normally split and given half in the morning and half in the evening.

How much to take
Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition.
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day.
- This may be increased to 2500mg each day depending on your illness.

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness.
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day.
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness.

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day.
- Depending on the child's condition your child's doctor may decide to increase this dose.

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose.

Patients taking other medicines for fits (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim. If so, your doctor should gradually initiate treatment depending on your or your child's condition.
- Your doctor may increase the dose of Epilim by 5-10mg for each kilogram of body weight each day depending on which other medicines you are taking.

If you take more Epilim than you should
If you take more Epilim than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Epilim
Keep taking until your doctor tells you to stop. Do not stop taking Epilim just because you feel better. If you stop your fits may come back.

Tests
Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. Epilim can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- You have an **allergic reaction.** The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim. It includes feeling and being sick many times; being very tired, sleepy and weak; stomach pain including very bad upper stomach pain; jaundice (yellowing of the skin or whites of the eyes); loss of appetite; swelling (especially of the legs and feet but may include other parts of the body); worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Epilim immediately if you have these symptoms.
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'.
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'.
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'.
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason.
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma).

- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma).
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion).

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyperactive and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim starting dose is high or has been suddenly increased.
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert.
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements.
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits.
- Blisters with the skin flaking away.
- Rapid, uncontrollable movement of the eyes.
- An increase in the number and severity of convulsions.

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick (nausea), being sick (vomiting), stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food.
- Swelling of gums or sore mouth
- Fainting
- Hearing loss
- Nail and nail bed disorders
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine.
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before.
- Hair disorders (changes in texture, colour or growth)
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain – as your appetite may be increased
- Kidney disease
- Kidney problems, bedwetting or increased need to pass urine
- Blood in the urine
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)
- Obesity

Bone disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Blood tests
Epilim can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male fertility
Taking Epilim can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

United Kingdom
You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta
You can also report side effects directly via ADR Reporting: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epilim

Keep out of the sight and reach of children.
Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the last day of that month.
Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips.
Store in a dry place below 30°C.
Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.
These measures will help protect the environment.

6. Contents of the pack and other information

What Epilim Gastro-resistant Tablets contain
- Each 200mg gastro-resistant tablet contains 200mg of the active substance, sodium valproate.
- Each 500mg gastro-resistant tablet contains 500mg of the active substance, sodium valproate.
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid monohydrate (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hydroxypropyl cellulose (E463).

What Epilim Gastro-resistant Tablets look like and contents of the pack
Epilim tablets are round and lilac coloured. The tablets are supplied in blister packs of 30 or 100.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis S.A,
Carretera C-35 (La Batlloria-Hostalric), Km 63.09
17404 Riells i Viabrea (Girona), Spain

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in June 2018

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050
Website: www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400
Website: www.epilepsynse.org.uk

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Epilim® 200mg and 500mg Gastro-resistant Tablets

sodium valproate

SANOFI

Is this leaflet hard to see or read? Phone 0845 372 7101 for help.

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING

Epilim, sodium valproate, can seriously harm an unborn baby when taken during pregnancy. If you are a female able to have a baby you must use an effective method of birth control (contraception) without interruption during your entire treatment with Epilim. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.

Do not stop taking Epilim unless your doctor tells you to as your condition may become worse.

If you are a parent or caregiver of a female child treated with Epilim, you must also read section 2 of this leaflet carefully and contact your child's doctor once they experience their first period.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epilim is and what it is used for

What Epilim is
The name of your medicine is Epilim 200mg or 500mg Gastro-resistant Tablets (called Epilim in this leaflet). Epilim 200mg or 500mg Gastro-resistant Tablets are "enteric coated" this means that the tablets have a protective coating that allows them to reach the intestines (gut) without being dissolved in the stomach first. This helps stop them from causing a stomach upset.

What Epilim contains
Epilim contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim is used for
Epilim is used to treat epilepsy (fits) in adults and children.

2. What you need to know before you take Epilim

Do not take Epilim and tell your doctor if:
X You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim (see Section 6: Contents of the pack and other information). Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
X You have liver problems or you or your family have a history of liver problems.
X You have a rare illness called porphyria.
X You have a known metabolic disorder, i.e. a urea cycle disorder.
X You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
X You are pregnant, unless nothing else works for you (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).

If you are a woman able to have a baby you must not take Epilim unless you use an effective method of birth control (contraception) at all times during your treatment with Epilim. Do not stop taking Epilim or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim.

Warnings and precautions
- A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking Epilim if:
▲ You have diabetes. This medicine may affect the results of urine tests.
▲ You have a carnitine palmitoyltransferase type II deficiency.
▲ You have kidney problems. Your doctor may give you a lower dose.
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body.
▲ You have an illness called 'systemic lupus erythematosus (SLE)' – a disease of the immune system which affects skin, bones, joints and internal organs.
▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim.

Weight gain
Taking Epilim may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim and during your treatment.

Other medicines and Epilim
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim can affect the way some other medicines work. Also some medicines can affect the way Epilim works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim:
- Some medicines used for pain and inflammation (salicylates) such as aspirin.
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, 'Patients taking other medicines for fits'. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate.

Epilim may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin).
- Zidovudine – used for HIV infection.
- Temozolomide used to treat cancer.
- Medicines for depression.
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.
- Nimodipine.
- Propofol – used for anaesthesia.

The following medicines can affect the way Epilim works:
- Oestrogen-containing products (including some birth control pills).
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine.
- Cimetidine – used for stomach ulcers.
- Protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim and carbapenems should be avoided because it may decrease the effect of your medicine.
- Cholestyramine used to lower blood fat (cholesterol) levels.

Taking Epilim with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women
- You must not use Epilim if you are pregnant, unless nothing else works for you.
- If you are a woman able to have a baby, you must not take Epilim unless you use an effective method of birth control (contraception) during your entire treatment with Epilim.
- Do not stop taking Epilim or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy
- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:
- **I AM STARTING TREATMENT WITH EPILIM**
- **I AM TAKING EPILIM AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING EPILIM AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING EPILIM**

I AM STARTING TREATMENT WITH EPILIM
If this is the first time you have been prescribed Epilim your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with Epilim. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- Pregnancy must be excluded before start of treatment with Epilim with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Epilim.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING EPILIM AND NOT PLANNING TO HAVE A BABY
If you are continuing treatment with Epilim but you are not planning to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Epilim. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with Epilim.
- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING EPILIM AND PLANNING TO HAVE A BABY
If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking Epilim or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development, which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of Epilim, switch you to another medicine, or stop treatment with Epilim a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking Epilim unless your doctor tells you to.
- Do not stop using your birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine or stop treatment with Epilim a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING EPILIM
Do not stop taking Epilim unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of epilepsy so that alternative treatment options can be evaluated.

In the exceptional circumstances when Epilim is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking Epilim unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Epilim during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the Patient Guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
Very little Epilim gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may feel sleepy when taking Epilim. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim

Always take Epilim exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Epilim treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine
- Your doctor will decide how much Epilim to give you or your child depending on your or your child's body weight.
- Take this medicine by mouth.
- **Do not** crush or chew the tablets.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor.

How to take this medicine
- The dose is normally split and given half in the morning and half in the evening.

How much to take
Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition.
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day.
- This may be increased to 2500mg each day depending on your illness.

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness.
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day.
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness.

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day.
- Depending on the child's condition your child's doctor may decide to increase this dose.

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose.

Patients taking other medicines for fits (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim. If so, your doctor should gradually initiate treatment depending on your or your child's condition.
- Your doctor may increase the dose of Epilim by 5-10mg for each kilogram of body weight each day depending on which other medicines you are taking.

If you take more Epilim than you should
If you take more Epilim than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Epilim
Keep taking until your doctor tells you to stop. Do not stop taking Epilim just because you feel better. If you stop your fits may come back.

Tests
Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. Epilim can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- You have an **allergic reaction.** The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim. It includes feeling and being sick many times; being very tired, sleepy and weak; stomach pain including very bad upper stomach pain; jaundice (yellowing of the skin or whites of the eyes); loss of appetite; swelling (especially of the legs and feet but may include other parts of the body); worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Epilim immediately if you have these symptoms.
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'.
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'.
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'.
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason.

Depakote – summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. Trade Name of the Medicinal Product

Depakote 250mg Tablets.

2. Qualitative and Quantitative Composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

3. Pharmaceutical Form

Gastro-resistant tablets.

Clinical Particulars

4.1. Therapeutic Indications

Depakote is indicated for the acute treatment of the manic episode associated with bipolar disorder.

4.2. Posology and Method of Administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not chewed.

The daily dosage should be established according to age and body weight. The wide individual sensitivity to valproate semisodium should also be considered.

There is no clear correlation between daily dose, plasma concentration and therapeutic effect. Optimum dosage should be determined mainly by clinical response. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected.

In mania it is generally agreed that plasma levels around 45 to 50µg/ml are needed to allow efficacy; most patients receiving Depakote during controlled clinical trials achieved maximum plasma concentration of greater than 75µg/ml.

Dosage

Adults
The recommended initial dose is 750mg daily in 2 to 3 divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses usually range between 1000 and 2000mg.
Patients receiving daily doses higher than 45mg/kg should be carefully monitored.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

For use in patients with liver or renal disease, see 4.3 'Contraindications' and 4.4 'Special Warnings and Special Precautions for Use'.

4.3. Contra-indications

Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Active liver disease.
Personal or family history of severe hepatic dysfunction, especially drug related.
Porphyria.

4.4. Special Warnings and Precautions for Use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Special Warnings

Hepatic
Severe liver damage resulting sometimes in fatalities has exceptionally been reported. Experience in epilepsy has indicated that patients most at risk are children under the age of three with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disorders. The incidents mainly occurred during the first 6 months of therapy, and usually involved multiple therapy. After the age of three, the incidence is significantly reduced and decreases progressively with age.

Clinical symptoms are essential for early diagnosis. In particular, aesthenia, anorexia, lethargy, drowsiness, which are usually of sudden onset and sometimes associated with repeated vomiting and abdominal pain, should be taken into consideration, especially in patients at risk. Patients (or their family) should be instructed to report immediately any such signs to the clinician should they occur. Investigations, including clinical examination and biological assessment of liver function, should be undertaken immediately.

Liver function should be assessed before therapy and periodically during the first six months. Tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors, increased bilirubin level and raised transaminases) requires cessation of treatment. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Pancreatitis

Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Depakote should be discontinued if pancreatitis is diagnosed.

Precautions

Liver function tests should be carried out before therapy and periodically during the first 6 months especially in patients at risk. Increased liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated, without clinical sign. More extensive biological investigations (including prothrombin rate) are recommended in these patients. An adjustment in dosage may be considered when appropriate, and tests should be repeated as necessary.

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

In patients with *renal insufficiency*, it may be necessary to decrease dosage according to clinical monitoring.

Although *immune disorders* have been only exceptionally noted during the use of valproate, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus.

When a urea cycle enzymatic deficiency is suspected, metabolic investigation should be performed prior to treatment because of the risk of *hyperammonaemia* with Depakote.

Diabetic patients: Depakote is eliminated mainly throughout the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5. Interactions with other Medicaments and other forms of Interaction

Effects of Depakote on other drugs

- *Clozapine, haloperidol, lithium*
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

- *Antipsychotics, MAO inhibitors, antidepressants, benzodiazepines*
Depakote may potentiate the effects of neuroleptics, monoamine oxidase inhibitors, anti-depressants and benzodiazepines. Clinical monitoring is advised and dosage should be adjusted when appropriate.

- *Carbamazepine*
The toxic effect of carbamazepine may be potentiated. Clinical monitoring is advised particularly at the beginning of combined therapy, and dosage should be adjusted when appropriate.

- *Lamotrigine*
Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Depakote might increase the risk of rash.

- *Phenobarbitone*
Depakote increases phenobarbitone plasma levels (due to inhibition of hepatic catabolism) and sedation may occur. The dose should be reduced immediately. Clinical monitoring is

recommended throughout the first two weeks of combined treatment and determination of phenobarbitone plasma levels when appropriate.

- *Primidone*
Depakote increases primidone plasma levels with exacerbation of adverse effects such as sedation. These signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy, with dosage adjustment when appropriate.

- *Phenytoin*
Depakote increases phenytoin total plasma concentration, and increases phenytoin free form with possible overdosage symptoms (Depakote displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- *Zidovudine*
Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.

Depakote has not appreciable enzyme-inducing effects and the efficacy *of oral contraceptive* agents does not appear to be affected.

Effects of other drugs on Depakote

Anticonvulsants with enzyme-inducing effects (e.g. phenytoin, phenobarbitone, carbamazepine) decrease serum valproic acid concentrations. Dosage should be adjusted according to blood levels.

Felbamate may increase serum valproic acid concentration. This should be monitored.

Mefloquine may increase valproic acid metabolism. Dosage should be adjusted according to blood levels.

Highly protein bound agents such as salicylates, may increase valproate free serum valproic acid levels. Protein-binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.

Cimetidine (but not ranitidine) and erythromycin may increase valproate serum levels as a result of reduced hepatic metabolism.

Cholestyramine may decrease the absorption of Depakote.

Carbapenem antibiotics may cause a rapid decrease in serum valproic acid concentration, and close monitoring of valproic acid levels is recommended.

4.6. Pregnancy and Lactation

When used for the treatment of manic episodes the benefits of therapy should be carefully weighed against risk in treating or counselling women of childbearing potential. If Depakote is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus.

When Depakote therapy is continued during pregnancy, precautions should be taken as described below.

Experience of the use of valproate-containing products during pregnancy has been gained during the treatment of epileptic mothers.

An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring

born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing Depakote treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound and other techniques if appropriate.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia. Afibrinogenaemia has also been reported and may be fatal. Hypofibrinogenaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbitone and other enzyme-inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding
The concentration of serum valproic acid found in breast milk is very low, between 1% and 10% of total maternal plasma levels. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

4.7. Effects on Ability to Drive and Use Machines

Patients should be warned of the risk of drowsiness especially in cases of polytherapy or association with benzodiazepines (See 4.5 Interactions).

4.8. Undesirable Effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Hepatic
Rare cases of liver dysfunction (See 4.4.1 Special Warnings).

Teratogenic
Teratogenic risk (See 4.6 Pregnancy).

Neurological
Confusion: a few cases of altered levels of consciousness sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbitone) or after a sudden increase in valproate doses.

Very rare cases of reversible parkinsonism or reversible dementia associated with reversible cerebral atrophy have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Transient and/or dose related undesirable effects have often been reported: hair loss, fine postural tremor and drowsiness.

Gastrointestinal
Digestive disorders (nausea, gastralgia) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Hematological
Isolated reduction of fibrinogen or increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second stage of platelet aggregation). Haematological side effects including frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia have been reported.

Pancreatic
Very rare cases of pancreatitis, sometimes fatal, have been reported (see section 4.4.1 Special Warnings).

Renal
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with sodium valproate therapy, but the mode of action is as yet unclear.

Metabolic
Isolated and moderate hyperammonaemia without changes in liver function tests may occur frequently, and should not cause treatment discontinuation. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered. (See 4.4.2 Precautions).

Endocrine
Amenorrhoea and irregular periods have also been reported. Very rarely gynaecomastia has occurred.

Dermatological
Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Other
An increase in weight is not uncommon. The occurrence of vasculitis has been reported. Allergic reactions have been reported.

4.9. Overdose

Clinical signs of acute massive overdose usually include coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions. Deaths have occurred, however a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cerebral oedema and intracranial hypertension have been reported.

Hospital management of overdose should include gastric lavage (useful up to 10 to 12 hours following ingestion), osmotic diuresis, cardiac and respiratory monitoring. In very severe cases

dialysis or exchange transfusion may be performed. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Depakote exerts its effects mainly on central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two 3-week double-blind placebo controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2. Pharmacokinetic Properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food delays T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces valproic acid concentrations by about 20%.

5.3. Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical Particulars

6.1. List of Excipients

Colloidal silica, hydrated; Starch pregelatinised; Povidone; Titanium dioxide (E171); Talc; Hydroxypropylmethylcellulose phthalate; Diacetylated monoglycerides; Sunset yellow aluminium lake (E110); Vanillin.

6.2. Incompatibilities

Not relevant.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

None.

6.5. Nature and Contents of Container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

6.6. Instruction for Use/Handling

None.

Administrative Data

7. Marketing Authorisation Holder

Sanofi Winthrop Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom

Trading as:
Sanofi Synthelabo
P O Box 597
Guildford
Surrey

8. Marketing Authorisation Number

PL 11723/0251

9. Date of First Authorisation/Renewal of Authorisation

21 December 2000

10. Date of (Partial) Revision of the Text

Summary of Product Characteristics

Product Summary

1 Trade Name of the Medicinal Product

Depakote 250mg Tablets.

2 Qualitative and Quantitative Composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

3 Pharmaceutical Form

Gastro-resistant tablets.

Clinical Particulars

4.1 Therapeutic Indications

Depakote is indicated for the acute treatment of a manic episode associated with bipolar disorder.

4.2 Posology and Method of Administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not chewed.

The daily dosage should be established according to age and body weight. The wide individual sensitivity to valproate semisodium should also be considered.

There is no clear correlation between daily dose, plasma concentration and therapeutic effect. Optimum dosage should be determined mainly by clinical response. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected.

In mania it is generally agreed that plasma levels around 45 to 50μg/ml are needed to allow efficacy; most patients receiving Depakote during controlled clinical trials achieved a maximum plasma concentration of greater than 75μg/ml.

Dosage

Adults
The recommended initial dose is 750mg daily in 2 to 3 divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses usually range between 1000 and 2000mg.

Patients receiving daily doses higher than 45mg/kg should be carefully monitored.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

For use in patients with liver or renal disease, see 4.3 'Contraindications' and 4.4 'Special Warnings and Special Precautions for Use'.

4.3 Contraindications

Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Active liver disease.
Personal or family history of severe hepatic dysfunction, especially drug related.
Porphyria.

4.4 Special Warnings and Precautions for Use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

4.4.1 Special Warnings

Hepatic
Severe liver damage sometimes resulting in fatalities has exceptionally been reported. Experience in epilepsy has indicated that patients most at risk are children under the age of three with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disorders. These incidents mainly occurred during the first 6 months of therapy, and usually involved multiple therapy. After the age of three, the incidence is significantly reduced and decreases progressively with age.

Clinical symptoms are essential for early diagnosis. In particular, aesthenia, anorexia, lethargy, drowsiness, which are usually of sudden onset and sometimes associated with repeated vomiting and abdominal pain, should be taken into consideration, especially in patients at risk. Patients (or their family) should be instructed to report immediately any such signs to the clinician should they occur. Investigations, including clinical examination and biological assessment of liver function, should be undertaken immediately.

Liver function should be assessed before therapy and periodically during therapy. Tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors, increased bilirubin level and raised transaminases) requires cessation of treatment. Any concomitant use of salicylates should be stopped since they use the same metabolic pathway.

Pancreatitis
Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children, and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting). Medical evaluation (including measurement of serum amylase) should be undertaken in patients presenting with symptoms suggestive of pancreatitis. Depakote should be discontinued if pancreatitis is diagnosed.

Weight gain:
Depakote very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain.

4.4.2 Precautions

Liver function tests should be carried out before therapy and periodically during therapy especially in patients at risk. Increased liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated, without clinical sign. More extensive biological investigations (including prothrombin rate) are recommended in these patients. An adjustment in dosage may be considered when appropriate, and tests should be repeated as necessary.

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

In patients with *renal insufficiency*, it may be necessary to decrease dosage according to clinical monitoring.

Although *immune disorders* have been only exceptionally noted during the use of valproate, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus.

When a urea cycle enzymatic deficiency is suspected, metabolic investigation should be performed prior to treatment because of the risk of *hyperammonaemia* with Depakote.

Pregnancy: Women of child-bearing potential, should receive specialist psychiatric advice prior to starting Depakote and if planning a pregnancy whilst taking Depakote because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

4.5.1 Effects of Depakote on other drugs

- *Clozapine, haloperidol, lithium*
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

-*Antipsychotics, MAO inhibitors, antidepressants, benodiazepines*
Depakote may potentiate the effects of antipsychotics, monoamine oxidase inhibitors, anti-depressants and benzodiazepines. Clinical monitoring is advised and dosage should be adjusted when appropriate.

- *Carbamazepine*
The toxic effect of carbamazepine may be potentiated. Clinical monitoring is advised particularly at the beginning of combined therapy, and dosage should be adjusted when appropriate.

- *Lamotrigine*
Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Depakote might increase the risk of rash.

- *Phenobarbitone*
Depakote increases phenobarbitone plasma levels (due to inhibition of hepatic catabolism) and sedation may occur. The dose should be reduced immediately. Clinical monitoring is recommended throughout the first two weeks of combined treatment and determination of phenobarbitone plasma levels when appropriate.

- *Primidone*
Depakote increases primidone plasma levels with exacerbation of adverse effects such as sedation. These signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy, with dosage adjustment when appropriate.

- *Phenytoin*
Depakote decreases phenytoin total plasma concentration, and increases phenytoin free form with possible overdosage symptoms (Depakote displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- *Warfarin*
Protein-binding of warfarin and other coumarin anticoagulants may be reduced. The prothrombin time should be closely monitored.

- *Zidovudine*
Zidovudine plasma concentration may be raised leading to increased zidovudine toxicity.

Depakote has no appreciable enzyme-inducing effects and the efficacy *of oral contraceptive agents* does not appear to be affected.

4.5.2 Effects of other drugs on Depakote

Anticonvulsants with enzyme-inducing effects (e.g. phenytoin, phenobarbitone, carbamazepine) decrease serum valproic acid concentrations. Dosage should be adjusted according to blood levels.

Felbamate may increase serum valproic acid concentration. This should be monitored.

Mefloquine may increase valproic acid metabolism. Dosage should be adjusted according to blood levels.

Highly protein bound agents such as salicylates, may increase free serum valproic acid levels.

Cimetidine (but not ranitidine) and erythromycin may increase serum valproic acid levels as a result of reduced hepatic metabolism.

Cholestyramine may decrease the absorption of Depakote.

Carbapenem antibiotics may cause a rapid decrease in serum valproic acid concentration, and close monitoring of valproic acid levels is recommended.

4.6 Pregnancy and Lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

- Risk associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers treated with valproate.

Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

- In view of the above data

Women of childbearing age should be informed of the risks and benefits of continuing Depakote treatment throughout pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the is preferable in order to avoid high peak plasma levels.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation.

Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned of the risk of drowsiness especially in cases of polytherapy or association with benzodiazepines (See 4.5 Interactions).

4.8 Undesirable Effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Hepatic
Rare cases of liver dysfunction (See 4.4.1 Special Warnings).

Teratogenic
Teratogenic risk (See 4.6 Pregnancy).

Neurological
Confusion; a few cases of altered levels of consciousness sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbitone) or after a sudden increase in sodium valproate doses.

Very rare cases of reversible parkinsonism or reversible dementia associated with reversible cerebral atrophy have been reported.

Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Transient and/or dose related undesirable effects have often been reported: hair loss, fine postural tremor and drowsiness.

Gastrointestinal
Appetite may increase and Depakote very commonly causes weight gain which may be marked and progressive. (see section 4.4 Special Warnings and Special Precautions for Use). Digestive disorders (nausea, gastralgia) frequently occur at the

start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Haematological
Isolated reduction of fibrinogen or increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second stage of platelet aggregation). Haematological side effects including frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia have been reported.

Pancreatic
Very rare cases of pancreatitis, sometimes fatal, have been reported (see section 4.4.1 Special Warnings).

Renal
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with sodium valproate therapy, but the mode of action is as yet unclear.

Metabolic
Isolated and moderate hyperammonaemia without changes in liver function tests may occur frequently, and should not cause treatment discontinuation. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered. (See 4.4.2 Precautions).

Endocrine
Amenorrhoea and irregular periods have also been reported. Very rarely gynaecomastia has occurred.

Dermatological
Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported. Hirsutism and acne have been very rarely reported.

Other
The occurrence of vasculitis has been reported. Allergic reactions have been reported.

4.9 Overdose

Clinical signs of acute massive overdose usually include coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions. Deaths have occurred, however a favourable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cerebral oedema and intracranial hypertension have been reported.

Hospital management of overdose should include gastric lavage (useful up to 10 to 12 hours following ingestion), osmotic diuresis, cardiac and respiratory monitoring. In very severe cases dialysis or exchange transfusion may be performed. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic Properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical Particulars

6.1 List of Excipients

Colloidal silica, hydrated; Starch pregelatinised; Povidone; Titanium dioxide (E171); Talc; Hypromellose phthalate; Diacetylated monoglycerides; Sunset yellow aluminium lake (E110); Vanillin.

6.2 Incompatibilities

Not relevant.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

None.

6.5 Nature and Contents of Container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

6.6 Instruction for Use/Handling

None.

Administrative Data

7 Marketing Authorisation Holder

Sanofi-Synthelabo Limited
One Onslow Street
Guildford
Surrey
GU1 4YS

Trading as:
Sanofi-Synthelabo
PO Box 597
Guildford
Surrey

8 Marketing Authorisation Number

11723/0251

9 Date of First Authorisation/Renewal of Authorisation

21 December 2000

10 Date of (Partial) Revision of the Text

April 2003

Summary of Product Characteristics

Product Summary

1 Trade Name of the Medicinal Product

Depakote 250mg Tablets.

2 Qualitative and Quantitative Composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

3 Pharmaceutical Form

Gastro-resistant tablets.

CLINICAL PARTICULARS

4.1 Therapeutic Indications

Depakote is indicated for the acute treatment of a manic episode associated with bipolar disorder.

4.2 Posology and Method of Administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not chewed.

The daily dosage should be established according to age and body weight. The wide individual sensitivity to valproate semisodium should also be considered.

There is no clear correlation between daily dose, plasma concentration and therapeutic effect. Optimum dosage should be determined mainly by clinical response. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected.

In mania it is generally agreed that plasma levels around 45 to 50µg/ml are needed to allow efficacy; most patients receiving Depakote during controlled clinical trials achieved a maximum plasma concentration of greater than 75µg/ml.

Dosage

Adults
The recommended initial dose is 750mg daily in 2 to 3 divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses usually range between 1000 and 2000mg.
Patients receiving daily doses higher than 45mg/kg should be carefully monitored.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special Warnings and Precautions for Use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate.
Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.
Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects)

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of valproate, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive.
Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of child-bearing potential, should receive specialist psychiatric advice prior to starting Depakote and if planning a pregnancy whilst taking Depakote because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

4.5.1 Effects of Depakote on other drugs

- *Clozapine, haloperidol, lithium*

No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

- *Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines*
Valproate may potentiate the effect of antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- *Phenobarbital*
Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- *Primidone*
Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- *Phenytoin*
Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- *Carbamazepine*
Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- *Lamotrigine*
Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Depakote might increase the risk of rash.

- *Zidovudine*
Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- *Vitamin K-dependent anticoagulants*
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

4.5.2 Effects of other drugs on Depakote

Anticonvulsants with enzyme inducing effects (including *phenytoin, phenobarbital, carbamazepine*) decrease valproic acid plasma concentrations.

Dosages should be adjusted according to blood levels in case of combined therapy.
On the other hand, combination of *felbamate* and valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

Mefloquine and *Chloroquine* increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of valproate and *highly protein bound agents (e.g. aspirin)*, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with *cimetidine* or *erythromycin*

Carbapenem antibiotics such as *imipenem* and *meropenem* : Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood level is recommended.

Cholestyramine may decrease the absorption of valproate.

4.5.3 Other Interactions

Valproate usually has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving horminal contraception, including the oral contraceptive pill.

4.6 Pregnancy and Lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:
- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.
There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers treated with valproate.
Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.
Epidemiological studies, of women with epilepsy, have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment.

- In view of the above data

Women of childbearing age should be informed of the risks and benefits of continuing Depakote treatment throughout pregnancy.
Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.
Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.
Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable Effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.
Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.
Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: cutaneous reactions such as exanthematous rash rarely occur with valproate. In very rare cases, toxic

epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Immune system disorders: allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Clinical signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratotgastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.
Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.
Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic Properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Colloidal silica, hydrated; Starch pregelatinised; Povidone; Titanium dioxide (E171); Talc; Hypromellose phthalate; Diacetylated monoglycerides; Sunset yellow aluminium lake (E110); Vanillin.

6.2 Incompatibilities

Not relevant.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

None.

6.5 Nature and Contents of Container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

6.6 Instruction for Use/Handling

None.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Synthelabo Limited
One Onslow Street
Guildford
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GU1 4YS

Trading as:
Sanofi-Synthelabo
PO Box 597
Guildford
Surrey

8 MARKETING AUTHORISATION NUMBER

11723/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

21 December 2000

10 DATE OF (PARTIAL) REVISION OF THE TEXT

May 2004

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Depakote 250mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 Pharmaceutical form

250mg: Oval, orange gastro-resistant tablets.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose

should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.
When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a

pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- Antipsychotics , MAO inhibitors, antidepressants and benzodiazepines
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Clozapine, haloperidol, lithium
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- Lithium
Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine.

Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine
Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- Felbamate
Valproic acid may decrease the felbamate mean clearance by up to 16%.

- Zidovudine
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- Vitamin K-dependent anticoagulants
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- Temozolomide
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.
On the other hand, combination of ***felbamate*** and Depakote decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem, imipenem*** and ***meropenem***:
Decreases in blood levels of valproic acid have been reported when it is coadministered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).
Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.
When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")
In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- Risk associated with bipolar therapy
This drug should be withdrawn under specialist supervision.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects,

malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy.

If a women plans a pregnancy or becomes pregnant, Depakote therapy should be reassessed whatever the indication:
• In bipolar disorders indication, cessation of Depakote treatment should be considered.
• In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.
• Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly

above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.
Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

4.6.2 Lactation
Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of extrapyramidal symptoms which may not be reversible including reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder: Confusion has been reported

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.
Syndrome of inappropriate secretion of ADH (SIADH)

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including red cell aplasia.
Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an

indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: Rash rarely occurs with Depakote. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and dysmenorrhea have been reported. Very rarely gynaecomastia has occurred. Male infertility.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic, ATC code: N03AG01
Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total

concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 Pharmaceutical particulars

6.1 List of excipients

Depakote 250mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Sunset yellow aluminium lake (E110), Vanillin.

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 90 tablets.

6.6 Special precautions for disposal

No special requirements

7 Marketing authorisation holder

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 Marketing authorisation holder

Depakote 250 mg: 04425/0199

9 Date of the first authorisation or renewal

Date of latest renewal:
Depakote 250mg: 1 June 2009

10 Date of revision of the text

13 July 2011

Legal status

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Depakote 250mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 Pharmaceutical form

250mg: Oval, orange gastro-resistant tablets.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose

should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.
When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a

pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- Antipsychotics , MAO inhibitors, antidepressants and benzodiazepines
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Clozapine, haloperidol, lithium
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- Lithium
Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine.

Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.
On the other hand, combination of ***felbamate*** and Depakote decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem, imipenem*** and ***meropenem***:
Decreases in blood levels of valproic acid have been reported when it is coadministered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).
Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.
When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")
In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- Risk associated with bipolar therapy
This drug should be withdrawn under specialist supervision.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects,

malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy.

If a women plans a pregnancy or becomes pregnant, Depakote therapy should be reassessed whatever the indication:
• In bipolar disorders indication, cessation of Depakote treatment should be considered.
• In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.
• Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly

above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.
Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

4.6.2 Lactation
Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of extrapyramidal symptoms which may not be reversible including reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder: Confusion has been reported

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.
Syndrome of inappropriate secretion of ADH (SIADH)

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including red cell aplasia.
Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an

indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: Rash rarely occurs with Depakote. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and dysmenorrhea have been reported. Very rarely gynaecomastia has occurred. Male infertility.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic, ATC code: N03AG01
Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total

concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 Pharmaceutical particulars

6.1 List of excipients

Depakote 250mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Sunset yellow aluminium lake (E110), Vanillin.

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 90 tablets.

6.6 Special precautions for disposal

No special requirements

7 Marketing authorisation holder

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 Marketing authorisation holder

Depakote 250 mg: 04425/0199

9 Date of the first authorisation or renewal

Date of latest renewal:
Depakote 250mg: 1 June 2009

10 Date of revision of the text

13 July 2011

Legal status

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Depakote 250mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Oval, orange gastro-resistant tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in

combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.
When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)
Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.
Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,

These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Clozapine and haloperidol,***
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- ***Lithium***
Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- ***Phenobarbital***
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Depakote decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem, imipenem*** and ***meropenem:*** Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided

(section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).

Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.

When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- Risk associated with bipolar therapy
This drug should be withdrawn under specialist supervision.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73% (95% CI: 8.16 – 13.29). Available data indicate dose dependency of this effect.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data

The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a woman of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy.

If a woman plans a pregnancy or becomes pregnant, Depakote therapy should be reassessed whatever the indication:

- In bipolar disorders indication, cessation of Depakote treatment should be considered.
- In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.

- Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.

Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors; afibrinogenemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

4.6.2 Lactation

Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 1 %; Common ≥ 1 and ≤ 10 %; Uncommon ≥ 0.1 and ≤ 1 %; Rare ≥ 0.01 and ≤ 0.1 %; Very rare ≥ 0.01 %, Unknown (cannot be estimated from available data).

Congenital and familial/genetic disorders: (see section 4.6. Fertility, pregnancy and lactation)

Hepato-biliary disorders:
Common: liver injury (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders:
Very common: nausea,
Common: gastralgia, diarrhoea

The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Uncommon: pancreatitis, sometimes lethal, (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus,
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder:
Common: confusional state, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolic disorders:
Common: hyponatraemia.
Rare: hyperammonaemia* (see section 4.4.2 Precautions)

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions).
Uncommon: pancytopenia, leucopenia.

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia,agranulocytosis, anaemia macrocytic, macrocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash

Hirsutism and acne have been very rarely reported.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation).
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: Deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Rare: enuresis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: non-severe oedema peripheral

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depakote. The mechanism by which Depakote affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Common: Weight increased*
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4.2 Precautions)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Other Antipsychotics, ATC code: N05AX.

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica, hydrated
Starch pregelatinised
Povidone
Titanium dioxide (E171)
Talc
Hypromellose phthalate
Diacetylated monoglycerides
Sunset yellow aluminium lake (E110)
Vanillin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS, UK

8 MARKETING AUTHORISATION NUMBER(S)

04425/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2009
Date of latest renewal: 1 June 2009

10 DATE OF REVISION OF THE TEXT

28 November 2012

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Depakote 250mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Oval, orange gastro-resistant tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Female children, female adolescents, women of childbearing potential and pregnant women

Depakote should be initiated and supervised by a specialist experienced in the management of bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Depakote should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.
When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)
Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual

investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.
Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

Depakote should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Depakote plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Depakote during pregnancy (see section 4.6).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.

- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of bipolar disorder.

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data does not exclude the possibility of an increased risk for valproate semisodium.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Clozapine and haloperidol,
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- Lithium
Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Zidovudine***
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should

be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Depakote decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem, imipenem*** and ***meropenem:*** Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

Depakote should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children, female adolescents and woman of childbearing potential (see above and section 4.4)
If a Woman wants to plan a Pregnancy

- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of bipolar disorder. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

<u>Risk in the neonate</u>

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions

and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Depakote therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/ 10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from available data).
The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepato-biliary disorders:
Common: liver injury (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders:
Very common: nausea,
Common: gastralgia, diarrhoea

The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Uncommon: pancreatitis, sometimes lethal, (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus,
Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia.
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorder:
Common: confusional state, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolic disorders:
Common: hyponatraemia.
Rare: hyperammonaemia* (see section 4.4.2 Precautions)

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause

treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia, (see section 4.4.2 Precautions).
Uncommon: pancytopenia, leucopenia.

The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including red cell aplasia,agranulocytosis, anaemia macrocytic, macrocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash

Hirsutism and acne have been very rarely reported.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation).
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: Deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Rare: enuresis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: non-severe oedema peripheral

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depakote. The mechanism by which Depakote affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Common: Weight increased*
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4.2 Precautions)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.
Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.
In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Other Antipsychotics, ATC code: N05AX.
Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicone dioxide
Starch pregelatinised
Povidone
Titanium dioxide (E171)
Hypromellose
Polyethylene glycol 6000
Methacrylic acid- ethyl acrylate copolymer (1:1)

Triethyl citrate
Sunset yellow aluminium lake (E110)
Vanillin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

or trading as:-

Sanofi-aventis or Sanofi
One Onslow Street

Guildford
Surrey
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UK

8 MARKETING AUTHORISATION NUMBER(S)

04425/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2009
Date of latest renewal: 1 June 2009

10 DATE OF REVISION OF THE TEXT

5 February 2015

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Depakote 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Containing 269.10 mg of valproate semisodium* per tablet (equivalent to 250 mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Oval, orange gastro-resistant tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 – 2000 mg valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Female children and women of childbearing potential
Valproate must be initiated and supervised by a specialist experienced in the management of bipolar disorder. Valproate should not be used in female children or women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefit and risk should be carefully reconsidered at regular treatment reviews (see section 4.4).

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Combined Therapy
When starting Depakote in patients, already on anti-convulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 – 10 mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.

When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Depakote is contraindicated in the following situations:

- In pregnancy (see section 4.4 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
- Porphyria.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:
Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme
Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Depakote is contraindicated in the following situations:
- In pregnancy (see sections 4.3 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that:
- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment

by a specialist experienced in the management of bipolar disorder.

- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist

The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:
- The Patient Card is provided with every valproate dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder.

Aggravated convulsions:
As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and

behaviour. The mechanism of this risk is not known and the available data does not exclude the possibility of an increased risk for valproate semisodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

4.4.2 Precautions

Haematological:
Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus:
Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia:
When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote (see section 4.3).

Weight gain:

Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Diabetic patients:
Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomylosis when taking sodium valproate.

Alcohol:
Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
  Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

  In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Clozapine and haloperidol,***
  No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- ***Lithium***
  Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- ***Olanzapine***
  Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***
  Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
  Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
  Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
  Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
  Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Rufinamide***
  Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***
  Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***
  Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***
  In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
  Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Anti-epileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with ***phenytoin*** or ***phenobarbital.*** Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of ***felbamate*** and Depakote decreases valproic acid clearance by 22% – 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics (such as ***panipenem, imipenem*** and ***meropenem)***: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60% – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Protease inhibitors such as ***lopinavir*** and ***ritonavir*** decrease valproate plasma level when co-administered.

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***
  Co-administration of Depakote and quetiapine may increase the risk of neutropenia/leucopenia.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30 – 40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and section 4.4)

If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

Pregnant women
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Depakote therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/ 10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from available data).

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.
Uncommon: pancreatitis, sometimes lethal (see section 4.4 Special Warnings and Precautions for Use)

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus
Uncommon: coma*, encephalopathy*, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:
Common: hyponatraemia, weight increased*
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).
Rare: hyperammonaemia* (see section 4.4.2 Precautions), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia (see section 4.4.2 Precautions)
Uncommon: pancytopenia, leucopenia
Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation)
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depakote. The mechanism by which Depakote affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Depakote formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Other Antipsychotics, ATC code: N05AX.

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3 week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250 mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500 mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half-life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 – 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 – 0.6 L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 – 94% over plasma drug concentrations of 40 – 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicone dioxide
Starch pregelatinised
Povidone
Titanium dioxide (E171)
Hypromellose
Polyethylene glycol 6000
Methacrylic acid- ethyl acrylate copolymer (1:1)
Triethyl citrate
Sunset yellow aluminium lake (E110)
Vanillin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

or trading as:-

Sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2009
Date of latest renewal: 1 June 2009

10 DATE OF REVISION OF THE TEXT

30/04/2018

LEGAL STATUS

POM

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Depakote 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Containing 269.10 mg of valproate semisodium* per tablet (equivalent to 250 mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Oval, orange gastro-resistant tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage
Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 – 2000 mg valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see sections 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 and 4.4).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1).

Female children and women of childbearing potential
Valproate must be initiated and supervised by a specialist experienced in the management of bipolar disorder. Valproate should not be used in female children or women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefit and risk should be carefully reconsidered at regular treatment reviews (see section 4.4).

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Combined Therapy
When starting Depakote in patients, already on anti-convulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 – 10 mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.

When using Depakote with other psychotropics, a reduced dose may be required, (see section 4.5.1)

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

4.3 Contraindications

Depakote is contraindicated in the following situations:

- In pregnancy (see sections 4.4 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
- Porphyria.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the

patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:
Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme
Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Depakote is contraindicated in the following situations:
- In pregnancy (see sections 4.3 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that:
- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable

of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorder.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescriber must ensure that:
- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the

contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Oestrogen-containing products
Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (mood control) when initiating, or discontinuing oestrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:
- The Patient Card is provided with every valproate dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and

risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder.

Aggravated convulsions:
As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data does not exclude the possibility of an increased risk for valproate semisodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Carbapenem agents:
The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

4.4.2 Precautions

Haematological tests:
Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8).

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 and 5.2).

Patients with systemic lupus erythematosus:
Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8).

Urea cycle disorders:
When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote (see section 4.3).

Weight gain:
Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8).

Diabetic patients:
Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Carnitine palmitoyltransferase (CPT) type II deficiency:
Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomylosis when taking sodium valproate.

Alcohol:
Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- ***Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines***
  Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

  In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Clozapine and haloperidol***
  No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote.

- ***Lithium***
  Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium. Depakote has no effect on serum lithium levels.

- ***Olanzapine***
  Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***
  Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
  Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
  Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
  Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
  Depakote reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore clinical monitoring is recommended and dosage should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Felbamate***
  Valproic acid may decrease the felbamate mean clearance by up to 16%.

- ***Rufinamide***
  Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***

Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***
  Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Nimodipine***
  In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***Temozolomide***
  Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

- ***Anti-epileptics***
  Anti-epileptics with enzyme inducing effects (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

  Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

  On the other hand, combination of felbamate and Depakote decreases valproic acid clearance by 22% – 50% and consequently increase the valproic acid plasma concentrations. Depakote dosage should be monitored.

- ***Anti-malarial agents***
  Mefloquine and chloroquine increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

- ***Highly protein bound agents***
  In case of concomitant use of Depakote and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased.

- ***Vitamin K-dependent factor anticoagulants***
  The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Cimetidine or erythromycin***
  Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

- ***Carbapenem antibiotics (such as panipenem, imipenem and meropenem)***
  Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60% – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

- ***Rifampicin***
  Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors***
  Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered.

- ***Cholestyramine***
  Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

- ***Oestrogen-containing products, including oestrogen-containing hormonal contraceptives***
  Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

  On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

4.5.3 Other interactions

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***
  Co-administration of Depakote and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Valproate is contraindicated for use in women of childbearing potential unless the

conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Teratogenicity and developmental effects

Congenital malformations
Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30 – 40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and section 4.4)

Oestrogen-containing products
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4 and 4.5).

If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

Pregnant women
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Depakote therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/ 10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from available data).

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Hepatobiliary disorders:
Common: liver injury (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.
Uncommon: pancreatitis, sometimes lethal (see section 4.4 Special Warnings and Precautions for Use)

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus
Uncommon: coma*, encephalopathy*, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:
Common: hyponatraemia, weight increased*
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).
Rare: hyperammonaemia* (see section 4.4.2 Precautions), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Endocrine Disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)
Rare: hypothyroidism (see section 4.6 Fertility, pregnancy and lactation)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia (see section 4.4.2 Precautions)
Uncommon: pancytopenia, leucopenia
Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Fertility, pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage (see section 4.4.2 Precautions and 4.6 Fertility, pregnancy and lactation)
Uncommon: vasculitis

Ear and labyrinth disorders:
Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Uncommon: renal failure
Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depakote. The mechanism by which Depakote affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2 Precautions)

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

Investigations:
Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Depakote formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Antipsychotics; Other Antipsychotics, ATC code: N05AX.

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3 week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250 mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500 mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half-life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 – 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Plasma protein binding of Depakote ranges from 85 – 94% over plasma drug concentrations of 40 – 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

Metabolism

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 – 0.6 L/h and is independent of hepatic blood flow.

The major pathway of valproate biotransformation is glucuronidation (~40%), mainly via UGT1A6, UGT1A9, and UGT2B7.

Interaction with oestrogen-containing products

Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and

protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicone dioxide
Starch pregelatinised
Povidone
Titanium dioxide (E171)
Hypromellose
Polyethylene glycol 6000
Methacrylic acid- ethyl acrylate copolymer (1:1)
Triethyl citrate
Sunset yellow aluminium lake (E110)
Vanillin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

or trading as:
Sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2009
Date of latest renewal: 1 June 2009

10 DATE OF REVISION OF THE TEXT

31/08/2018

LEGAL STATUS

POM

Depakote – patient information leaflets

DEPAKOTE ® 250 mg TABLETS
DEPAKOTE ® 500 mg TABLETS

valproate semisodium
(also known as divalproex sodium USAN)

PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of this medicine is Depakote 250mg Tablets and Depakote 500mg Tablets.

What is in this medicine?

Each Depakote 250mg Tablet contains 269.1mg valproate semisodium (equivalent to 250mg valproic acid).

Each Depakote 500mg Tablet contains 538.2mg valproate semisodium (equivalent to 500mg valproic acid).

The tablets also contain colloidal silica (hydrated), starch (pregelantinised), povidone, titanium dioxide (E171), talc, hypromellose phthalate, diacetylated monoglycerides and vanillin. The 250mg tablets are coloured with sunset yellow (E110), and the 500mg tablets are coloured with Ponceau 4R (E124) and Indigo Carmine (E132).

Depakote 250mg Tablets are oval, orange tablets and Depakote 500mg Tablets are oval lilac tablets. They are supplied in packs of 90 tablets.

Depakote 250mg Tablets and Depakote 500mg Tablets are a mood stabilising medicine.

Product Licence holder: Sanofi-Synthelabo, PO Box 597, Guildford, Surrey, UK.

Manufactured by: Sanofi-Synthelabo SA, Carretera de la Batlloria a Hostalric KM 1,4 Riells I Viabrea Gerona, Spain.

What is this medicine for?

Depakote 250mg Tablets and Depakote 500mg Tablets are used to treat the manic phase of manic depression.

Before taking this medicine.

Depakote 250mg Tablets and Depakote 500mg Tablets should not be taken by patients with:

- liver problems
- a family history of liver problems
- a known allergy to Depakote Tablets/valproate semisodium or any of the other ingredients
- porphyria.

If you are diabetic Depakote 250mg Tablets and Depakote 500mg Tablets may make urine tests give false results.

Depakote and Pregnancy

Women who have to take Depakote 250mg Tablets or Depakote 500mg Tablets during the first 3 months of pregnancy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the early part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. There may also be blood clotting problems in the new born if the mother has taken Depakote 250mg Tablets or Depakote 500mg Tablets during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

Breast feeding: very little gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Depakote, or the effects of the other medicines, may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors.
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin - an antibiotic
- mefloquine - used to prevent malaria
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS.

When you first start taking Depakote 250mg Tablets or Depakote 500mg Tablets, or if you are taking it with other medicines, you may notice some drowsiness. If affected you should not drive or operate machinery.

The colourings in this medicine may cause allergic type reactions including asthma. This is more likely in patients who are allergic to aspirin.

Taking this medicine.

The usual dose is between 1000mg and 2000mg a day. This amount will be divided and taken in 2 or 3 doses throughout the day.

When treatment is first started you may be prescribed a lower dose (750mg). This is because some patients need less Depakote 250mg Tablets or Depakote 500mg Tablets than others to control their condition. Your doctor will increase

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Brand:	PRO DPKT 250/500 GB
Category:	LEAFLET
Argus Code:	021
Spec No:	668161
Supersedes:	668127
Core Spec No:	00000000
Ticket No:	SCP150
Date:	08.11.00
Issue No:	3
Operator:	KW
Page:	1 of 2
Unwind:	N/A
Size:	170 x 200 mm
Win/RFL Ref:	N/A
Barcode:	N/A
Mag:	N/A
BWR:	N/A

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No. colours and varnish: 2

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Signature:

Pharmacist/Medical Affairs
Approved: Yes ○ No ○ N/A ○
Date:
Signature:

Regulatory Affairs
Approved: Yes ○ No ○
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the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

Depakote 250mg Tablets and Depakote 500mg Tablets should not be used in patients less than 18 years of age.

If you have kidney problems your doctor may prescribe a lower dose.

Swallow the tablets whole with a drink of water, usually after meals. Do not chew.

If you forget to take a dose at the right time, take it as soon as you remember then go on as before.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Whilst taking this medicine.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Depakote 250mg Tablets or Depakote 500mg Tablets.

Depakote 250mg Tablets and Depakote 500mg Tablets can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment, and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, loss of appetite, jaundice (yellowing of the skin or whites of the eyes) or swelling of the legs. Your doctor may wish to do tests before you start treatment and for the first six months of treatment. Particular care is needed in those with other nervous system disease.

Depakote 250mg Tablets and Depakote 500mg Tablets sometimes cause the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Depakote 250mg Tablets and Depakote 500mg Tablets can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems, kidney problems or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Depakote 250mg Tablets and Depakote 500mg Tablets sometimes cause changes in the blood. You may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may cause tiredness; confusion; hallucinations; change in mood, jerky muscle movements and loss of consciousness. Rashes, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Depakote 250mg Tablets and Depakote 500mg Tablets.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also rarely immune disorders have occurred: if you have lupus, please tell your doctor before taking Depakote 250mg Tablets and Depakote 500mg Tablets.

Do not take this medicine after the month shown on the pack.

DATE OF REVISION OF LEAFLET:

October 2000

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

Depakote is a registered trademark.

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668161
170 x 200 mm

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Brand:	PRO DPKT 250/500 GB
Category:	LEAFLET
Argus Code:	021
Spec No:	668161
Supersedes:	668127
Core Spec No:	00000000
Ticket No:	SCP150
Date:	08.11.00
Issue No:	3
Operator:	KW
Page:	2 of 2
Unwind:	N/A
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Win/RFL Ref:	N/A
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BWR:	N/A

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Packaging Development
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Marketing
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Pharmacist/Medical Affairs
Approved: Yes ○ No ○ N/A ○
Date:
Signature:

Regulatory Affairs
Approved: Yes ○ No ○
Date:
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DEPAKOTE ® 250 mg TABLETS
DEPAKOTE ® 500 mg TABLETS

Valproate Semisodium
(also known as Divalproex Sodium USAN)

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- It is essential that you follow your doctor's advice.
- If you are helping someone else to take Depakote 250mg or 500mg Tablets, read this leaflet carefully before you give them the first dose.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

Each Depakote 250mg Tablet contains 269.1mg Valproate Semisodium (equivalent to 250mg Valproic Acid).
Each Depakote 500mg Tablet contains 538.2mg Valproate Semisodium (equivalent to 500mg Valproic Acid).
They also contain colloidal silica (hydrated), starch (pregelantinised), povidone, titanium dioxide (E171), talc, hypromellose phthalate, diacetylated monoglycerides and vanillin.
The 250mg tablets are coloured orange with sunset yellow (E110), and the 500mg tablets are coloured lilac pink with Ponceau 4R (E124) and Indigo Carmine (E132).
Product Licence holder: Sanofi-Synthelabo, PO Box 597, Guildford, Surrey
Manufactured by: Sanofi-Synthelabo SA, Carretera de la Batlloria a Hostalric KM 1, 4 Riells I Viabrea Gerona, Spain.

1. What is Depakote 250mg or 500mg Tablets and what are they used for?

Depakote 250mg Tablets and Depakote 500mg Tablets are a mood stabilising medicine and are used to treat the manic phase of manic depression.
Depakote 250mg Tablets are oval, orange tablets and Depakote 500mg Tablets are oval lilac pink tablets. They are supplied in packs of 90 tablets.

2. Before you take/use Depakote 250mg or 500mg Tablets

Do not take/use Depakote Tablets if you have:
- liver problems
- a family history of liver problems
- a known allergy Depakote Tablets/Valproate Semisodium or any of the other ingredients
- porphyria

Tell your doctor before starting Depakote Tablets if you
- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose

These statements apply to both present and past conditions.

Taking/using Depakote 250mg or 500mg Tablets with food and drink

Swallow the tablets whole with a drink of water, usually after meals. Do not chew.

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. It is essential that you discuss your treatment with your doctor well before you become pregnant. If at any time you suspect that you might already be pregnant you must tell your doctor immediately.
Women who take Depakote during the first month of pregnancy have a small risk (1-2%) of having a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. These can usually be detected in the first part of the pregnancy using routine antenatal screening blood tests and ultrasound scans. Rarely there may also be bleeding problems in the new born if the mother has taken Depakote during pregnancy.
Infants born to mothers who took Depakote during pregnancy may develop less quickly than normal. This may also be because of the mother's condition but the exact cause is not known.
It is important not to stop your Depakote suddenly as this is likely to result in you having fits which may harm both you and your baby.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. Very little gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

Driving and using machines

When you first start taking Depakote 250mg Tablets and Depakote 500mg Tablets, or if you are taking it with other medicines, you may notice some drowsiness. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Depakote 250mg Tablets and Depakote 500mg Tablets

The colourings in this medicine may cause allergic type reactions including asthma. This is more likely in patients who are allergic to aspirin.

Taking/using other medicines

The effects of valproate semisodium may also be changed by medicines taken some time ago, or it may change the effects of medicines you may take in the future. Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine – even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.

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Brand:	LLET DEPAKOTE TABLETS
Category:	LEAFLET
Argus Code:	47
Spec No:	668406
Supersedes:	00000
Ticket No:	SCP23318
Date:	29.09.03
Issue No:	5
Operator:	AL
Page:	1 of 2
Size:	170 x 200mm
Barcode:	N/A
Mag:	N/A
BWR:	N/A

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Fonts:

No. colours and varnish: 1

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Site of Manufacture
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Pharmacist/Medical Affairs
Approved: Yes ◯ No ◯ N/A ◯
Date:
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Regulatory Affairs
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Date:
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If taken with some other medicines the effects of Depakote 250mg Tablets and Depakote 500mg Tablets or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin - an antibiotic
- mefloquine and chloroquine - use to prevent and treat malaria - may increase the likelihood of a fit. Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS

3. How to take/use Depakote 250mg or 500mg Tablets

Swallow the tablets whole with a drink of water, usually after meals. Do not chew.

The usual dose is between 1000mg and 2000mg a day. This amount will be divided and taken in 2 or 3 doses throughout the day.

When treatment is first started you may be prescribed a lower dose (750mg). This is because some patients need less Depakote 250mg Tablets or Depakote 500mg Tablets than others to control their condition. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

Depakote 250mg Tablets and Depakote 500mg Tablets should not be used in patients less than 18 years of age.

If you have kidney problems your doctor may prescribe a lower dose.

Your doctor may wish to do tests before you start treatment and for the first six months of treatment.

If you take/use more Depakote 250mg or 500mg Tablets than you should:

An overdose of this medicine may be dangerous. If you think you or someone else may have taken/used more Depakote tablets than you should, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

If you forget to take/use Depakote 250mg or 500mg Tablets:

If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. However, you must take care not to take two doses at the same time.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Depakote 250mg Tablets or Depakote 500mg Tablets.

4. Possible side effects

Like all medicines, Depakote 250mg Tablets or Depakote 500mg Tablets can have side-effects. Depakote 250mg Tablets or Depakote 500mg Tablets can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness, especially if it is within the first six months of treatment, and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs.

Particular care is needed in those with other nervous system disease.

Whilst taking your tablets your appetite may be increased and you must take care to avoid weight gain.

Depakote 250mg Tablets or Depakote 500mg Tablets sometimes cause the following: nausea (usually relieved by taking tablets with or after food); vomiting; diarrhoea; changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching.

Depakote 250mg Tablets or Depakote 500mg Tablets sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely it may cause tiredness; confusion; hallucinations; change in mood, jerky muscle movements and loss of consciousness.

Occasionally Depakote 250mg Tablets or Depakote 500mg Tablets can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before.

Rashes sometimes severe, occur, rarely but patients who are also taking lamotrigine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Depakote 250mg Tablets or Depakote 500mg Tablets.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also, rarely immune disorders have occurred.

Very rarely it may also cause a change in women's periods, hearing problems, kidney problems, acne, increased hair growth in women or increased breast growth in men.

If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform you doctor or pharmacist.

5. Storing Depakote 250mg or 500mg Tablets

Keep your medicine in a safe place where children cannot reach it.

Do not take this medicine after the month shown on the pack.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date of revision of leaflet: October 2003.

Depakote is a registered trademark.

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668406
170 x 200 mm

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Seven Newcastle
Tel: (0044) 191 4917777

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BWR:	N/A

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Pharmacist/Medical Affairs
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DEPAKOTE ® 250 mg TABLETS
DEPAKOTE ® 500 mg TABLETS

Valproate Semisodium
(also known as Divalproex Sodium USAN)

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- **Keep this leaflet. You may need to read it again.**
- **It is essential that you follow your doctor's advice.**
- **If you are helping someone else to take Depakote 250mg or 500mg Tablets, read this leaflet carefully before you give them the first dose.**
- **If you have further questions, please ask your doctor or pharmacist.**
- **This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them even if their symptoms are the same as yours.**

In this leaflet:

Each Depakote 250mg Tablet contains 269.1mg Valproate Semisodium (equivalent to 250mg Valproic Acid).

Each Depakote 500mg Tablet contains 538.2mg Valproate Semisodium (equivalent to 500mg Valproic Acid).

They also contain colloidal silica (hydrated), starch (pregelantinised), povidone, titanium dioxide (E171), talc, hypromellose phthalate, diacetylated monoglycerides and vanillin.

The 250mg tablets are coloured orange with sunset yellow (E110), and the 500mg tablets are coloured lilac pink with Ponceau 4R (E124) and Indigo Carmine (E132).

Product Licence holder: Sanofi-Synthelabo, PO Box 597, Guildford, Surrey
Manufactured by: Sanofi-Synthelabo SA, Carretera de la Batlloria a Hostalric KM 1,4 Riells I Viabrea Gerona, Spain.

1. What is Depakote 250mg or 500mg Tablets and what are they used for?

Depakote 250mg Tablets and Depakote 500mg Tablets are a mood stabilising medicine and are used to treat the manic phase of manic depression.

Depakote 250mg Tablets are oval, orange tablets and Depakote 500mg Tablets are oval lilac pink tablets. They are supplied in packs of 90 tablets.

2. Before you take/use Depakote 250mg or 500mg Tablets

Do not take/use Depakote Tablets if you have:
- liver problems
- a family history of liver problems
- a known allergy to Depakote Tablets/Valproate Semisodium or any of the other ingredients
- porphyria (a rare metabolic condition)

Tell your doctor before starting Depakote Tablets if you
- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose

You should talk to your doctor or pharmacist even if you no longer have these conditions, but have had them in the past.

Your doctor may wish to do blood tests before you start and during the first six months of treatment.

Taking/using Depakote 250mg or 500mg Tablets with food and drink
Swallow the tablets whole with a drink of water, usually after meals. Do not crush or chew them.

Do not stop taking Depakote or change the number of tablets you are taking without first discussing this with your doctor, as this may lead to a recurrence of your symptoms.

When special care with Depakote 250mg or 500mg Tablets is needed
- if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe upper stomach pains, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your condition or a general feeling of being unwell. YOU SHOULD TELL YOUR DOCTOR IMMEDIATELY. Depakote can affect the liver (and rarely the pancreas) in a very small number of patients.

If you have any of the following speak to your doctor before starting your tablets:
- systemic lupus erythematosus (a rare disease),
- from any metabolic disorders, particularly hereditary enzyme deficiency disorders such as a urea cycle disorder because of a risk of increased ammonia level in the blood,
- impaired kidney function. Your doctor may want to monitor your blood valproate level or adapt your dose,
- an increased appetite and are putting on weight.

Pregnancy

Information for Women who could become Pregnant
Your doctor should discuss with you the problems that may arise if Depakote is used in pregnancy before you start treatment.

Unplanned pregnancy is not desirable in women receiving Depakote. You should use an effective method of contraception and consult your doctor before planning pregnancy. Depakote has no effect on the efficacy of your oral contraceptive pill.

It is known that women receiving Depakote during pregnancy have a higher risk than other women of giving birth to a child with an abnormality. The likelihood of abnormalities is increased if you are also taking antiepileptic medicines at the same time. These effects include:
- head and facial deformities including cleft palate – a gap or depression in the lip
- deformities of the bones including hip dislocation
- malformation of the limbs
- deformities of the urogenital tract including defects in the wall of the male urethra or vagina leading to an additional opening
- cardiovascular malformations, including heart defects
- defects in the lining of nerve tubes, such as holes or protrusions
- spina bifida

Women who take Depakote during pregnancy may be more likely to have a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. These can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Some babies born to mothers who took Depakote during pregnancy may develop less quickly than normal and may require additional educational support.

There may also be blood clotting problems (such as blood not clotting or not clotting very well) in the new born babies of mothers who have taken Depakote during pregnancy. This may appear as bruising or a delay in the stoppage of bleeds.

It is important not to stop your Depakote suddenly as this is likely to result in a relapse of your symptoms.

Information for Women who are planning to get Pregnant
If you become pregnant or think you may be pregnant whilst taking Depakote, you must tell your doctor immediately. Consult your doctor before planning pregnancy in order to receive appropriate counselling and to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy. It is essential that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Very little Depakote gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

Driving and using machines
When you first start taking Depakote 250mg Tablets and Depakote 500mg Tablets, or if you are taking it with other medicines such as anticonvulsants or benzodiazepines, you may notice some drowsiness. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Depakote 250mg Tablets and Depakote 500mg Tablets

The colourings in this medicine may cause allergic type reactions including asthma. This is more likely in patients who are allergic to aspirin.

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Taking/using other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine – even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.

If taken with some other medicines the effects of Depakote or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:
- colestyramine - used to treat high blood lipid (fat) levels
- antipsychotic agents (used to treat psychological disorders) - Depakote may increase the effects of these drugs.
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbital, lamotrigine, primidone, felbamate
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, carbapenem such as imipenem, panipenem and meropenem antibiotics
- mefloquine and chloroquine - use to prevent and treat malaria - may increase the likelihood of a fit. Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- temozolomide - used to treat cancer

When used in combination with olanzapine the following effects may occur; neutropenia – a blood disorder leading to a reduced chance of fighting infection, tremor, dry mouth, increased appetite and weight gain, problems with speech or sleepiness or extreme tiredness.

3. How to take/use Depakote 250mg or 500mg Tablets
Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Depakote 250mg Tablets or Depakote 500mg Tablets. Swallow the tablets whole (do not crush or chew them) with a drink of water, usually after meals. The usual dose is between 1000mg and 2000mg a day. This amount will be divided and taken in 2 or 3 doses throughout the day.

When treatment is first started you may be prescribed a lower dose (750mg). This is because some patients need less Depakote 250mg Tablets or Depakote 500mg Tablets than others to control their condition. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

Depakote 250mg Tablets and Depakote 500mg Tablets should not be used in patients less than 18 years of age.

If you have kidney problems your doctor may prescribe a lower dose.

If you take/use more Depakote 250mg or 500mg Tablets than you should:
An overdose of this medicine may be dangerous. If you think you may have taken more Depakote tablets than you should or someone else has taken some, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

If you forget to take/use Depakote 250mg or 500mg Tablets:
If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. However, you must not take two doses at the same time.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better, as this may lead to an immediate relapse. If you stop them your condition may get worse.

Make sure you keep your regular check-up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Depakote 250mg Tablets or Depakote 500mg Tablets.

4. Possible side effects
Like all medicines, Depakote 250mg Tablets or Depakote 500mg Tablets can have side-effects. Rarely they are serious, most of the time they are not. Usually they are reversible. You may need medical treatment if you get some of the side effects.

Tell your doctor IMMEDIATELY if you notice any of the following serious side effects. You may need urgent medical attention.
- repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe upper stomach pain, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs or a general feeling of being unwell.

Depakote 250mg Tablets or Depakote 500mg Tablets can affect the liver (and rarely the pancreas) in a very small number of patients.

You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment.

If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets.
- bizarre behaviour, an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration,
- blood clotting problems
- spontaneous bruising or bleeding
- blisters with skin detachment

If you experience any of the effects covered in this section, you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform you doctor or pharmacist.
- nausea or stomach ache, vomiting; diarrhoea; especially when starting the treatment,
- shakiness (tremor), drowsiness, unsteadiness when walking
- tiredness; confusion; hallucinations; change in mood
- jerky muscle movements
- loss of consciousness
- skin reactions such as rashes, occur, rarely but patients who are also taking lamotrigine may be more at risk
- nausea (usually relieved by taking tablets with or after food)
- changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching
- any loss of hair is usually temporary but when it grows back it may be more curly than before
- changes in women's period
- hearing problems
- acne
- increased hair growth in women
- increased breast growth in men
- allergic reactions
- swelling of the feet and legs (oedema)
- weight gain as your appetite may be increased
- kidney problems, bedwetting or increased need to pass urine
- immune disorders

These effects usually reverse on stopping the Depakote 250mg Tablets or Depakote 500mg Tablets.

Depakote 250mg Tablets or Depakote 500mg Tablets may cause a decrease in blood sodium which can result in tiredness, weakness, dizziness, feeling faint/fainting, nausea, vomiting and muscle cramps. Less commonly there may be bloating, swelling tightness of the hands and feet, confusion and seizures. Sometimes it can causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance.

5. Storing Depakote 250mg or 500mg Tablets
Keep your medicine in a safe place where children cannot see or reach it.

Do not take this medicine after the month shown on the pack.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date of revision of leaflet: April, 2005.

Depakote is a registered trademark.

The Manic Depression Fellowship is a charity which can provide more information about Manic Depression/Bipolar Disorder. They can be contacted at Manic Depression Fellowship Castle Works, 21 St. George's Road, London SE1 6ES.
Telephone: 08456 340 540.
Fax: 020 7793 2639.
Website: http://www.mdf.org.uk
E-mail: mdf@mdf.org.uk

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PACKAGE LEAFLET:
INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

Valproic acid (as valproate semisodium)

sanofi aventis

Is this leaflet hard to see or read?
Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

Depakote can be used to manage or control mania (feeling highly excited, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).

2. Before you take Depakote

Do not take Depakote and tell your doctor if:
- × You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see Section 6: Further information)
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- × You have liver problems
- × You or a family member has ever had liver problems caused by taking a medicine
- × You have a rare illness called porphyria which affects your metabolism

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Take special care with Depakote
A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking your medicine if:
- ▲ You are changing from another medicine that contains valproate
- ▲ The person taking this medicine is less than 18 years old
- ▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
- ▲ You have kidney problems
- ▲ You have problems with your pancreas
- ▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs
- ▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests)
- ▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain
Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:
- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:
- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Zidovine - used for HIV infection
- Some medicines used for infections such as panipenem, imipenem, and meropenem (carbapenem antibiotics), rifampicin or erythromycin
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Colestyramine - used for lowering blood cholesterol levels

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Women who could become pregnant
Before you start taking Depakote, your doctor should discuss with you the possible problems when it is taken in pregnancy.
- Unplanned pregnancy is not desirable in women taking Depakote
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.** Depakote has no effect on how well the oral contraceptive pill works.

  Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Depakote if you become pregnant. Women taking Depakote during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time.
  These abnormalities include:
  - Head and face deformities including cleft palate (a gap or depression in the lip)
  - Deformities of the bones, including hip dislocation
  - Malformations of the arms and legs
  - Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
  - Heart and blood vessel malformations with heart defects
  - Defects of the lining of the spinal cord
  - An abnormality of the spinal cord called 'Spina bifida'

Women who take Depakote during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Depakote may have babies with blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.

Some babies born to mothers who took Depakote during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Depakote if you want to become pregnant. Do not stop taking Depakote suddenly, as it is likely that your illness will come back.

Women who are planning to get Pregnant
If you become pregnant, think you may be pregnant or plan to become pregnant while taking Depakote, you must tell your doctor straight away.
- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding
If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines
You may feel sleepy, confused or dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote
Your medicine contains colours called **'sunset yellow aluminium lake (E110)'** and **'ponceau 4R aluminium lake (E124)'**. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

Turn Over

SCHAWK!

sanofi aventis

Brand:	DEPAKOTE 250/500 GB
Category:	LEAFLET
Argus Code:	166
Spec No:	678052
Supersedes:	00000
Ticket No:	273958
Date:	22.06.10
Issue No:	2
Operator:	JJ
Page:	1 of 2
Size:	170 x 315mm
Barcode:	N/A
Mag:	N/A
BWR:	N/A
BWR to be assigned by printer.	
Fonts:	OceanSans, ZapfDingbats
Product Logo Version: 000	
Minimum Point Size of Text: 8pt	
No. colours and varnish: 1	

Pantone Reflex Blue

678052

FOR SCHAWK USE ONLY

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3. How to take Depakote

Always take Depakote exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to take your medicine
- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take
The normal dose is:

Adults including the elderly
- **Starting dose** is 750mg on the first day. This is usually taken as 2 or 3 divided doses
- **The usual dose is then increased to** between 1000mg and 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems
- Your doctor may decide to lower your dose

Children
Depakote is not recommended for children and adolescents below 18 years of age

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (sezures), loss of consiousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose.

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:
- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells
- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

Other serious side effects which need urgent medical attention:
- Fits (seizures), loss of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath

Tell your doctor as soon as possible if you have any of the following side effects:
- Unusual behaviour including being very alert, and sometimes also aggressive, hyper-active and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days
- Hair, including body or facial hair, grows more than normal
- Temporary hair loss
- Acne
- Diarrohea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Bed wetting
- Weight gain

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Tell your doctor or pharmacist if any of the following side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.

Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Further Information

What Depakote 250mg Tablets contain
- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valporic acid)
- Hydrated colloidal silica, ,pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, sunset yellow aluminium lake (E110)

What Depakote 500mg Tablets contain
- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valporic acid)
- The other ingredients are: hydrated colloidal silica, pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, ponceau 4R aluminium lake (E124), indigo carmine aluminium lake (E132)

What Depakote looks like and contents of the pack
Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi-aventis, One Onslow Street, Guildford, Surrey, GU1 4YS UK
Tel: 01483 505515
Fax: 01483 535432
email: uk-medicalinformation@sanofi-aventis.com

Manufacturer
Sanofi Synthelabo SA, Carretera de la Batlloria a Hostalric KM 1, 4 Riells 1 Viabrea, Spain

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 05/2010

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SCHAWK!

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Category:	LEAFLET
Argus Code:	166
Spec No:	678052
Supersedes:	00000
Ticket No:	273958
Date:	22.06.10
Issue No:	2
Operator:	JJ
Page:	2 of 2
Size:	170 x 315mm
Barcode:	N/A
Mag:	N/A
BWR:	N/A
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Product Logo Version: 000	
Minimum Point Size of Text: 8pt	
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FOR SCHAWK USE ONLY

Pantone Reflex Blue

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PACKAGE LEAFLET:
INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

Valproic acid (as valproate semisodium)

sanofi aventis

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on
- to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).
Depakote can be used when lithium can not be used.

2. Before you take Depakote

Do not take Depakote and tell your doctor if:

x You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see Section 6: Further information)
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
x You have liver problems
x You or a family member has ever had liver problems caused by taking a medicine
x You have a rare illness called porphyria which affects your metabolism

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Take special care with Depakote

A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking your medicine if:

▲ You are changing from another medicine that contains valproate
▲ The person taking this medicine is less than 18 years old
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have kidney problems
▲ You have problems with your pancreas
▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs
▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests)
▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain

Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:

- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:

- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Zidovudine - used for HIV infection
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Colestyramine - used for lowering blood cholesterol levels

Taking Depakote with food and drink

Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding

You should not take this medicine if you are pregnant or a woman of child-bearing age unless explicitly advised by your doctor.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Women who could become pregnant

Before you start taking Depakote, your doctor should discuss with you the possible problems when it is taken in pregnancy.

- Unplanned pregnancy is not desirable in women taking Depakote
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.** Depakote has no effect on how well the oral contraceptive pill works.
  Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Depakote if you become pregnant. Women taking Depakote during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time.
  These abnormalities include:
  - Head and face deformities including cleft palate (a gap or depression in the lip)
  - Deformities of the bones, including hip dislocation
  - Malformations of the arms and legs
  - Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
  - Heart and blood vessel malformations with heart defects
  - Defects of the lining of the spinal cord
  - An abnormality of the spinal cord called 'Spina bifida'

Women who take Depakote during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Depakote may have babies with:

- blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar)

Some babies born to mothers who took Depakote during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.
Talk to your doctor before you stop taking Depakote if you want to become pregnant. Do not stop taking Depakote suddenly, as it is likely that your illness will come back.

Women who are planning to get Pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Depakote, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding

If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines

You may feel sleepy, confused or dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

Turn Over

Important information about some of the ingredients of Depakote
Your medicine contains colours called **'sunset yellow aluminium lake (E110)'** and **'ponceau 4R aluminium lake (E124)'**. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure.

How to take your medicine
- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take
The normal dose is:

Adults including the elderly
- **Starting dose** is 750mg on the first day. This is usually taken as 2 or 3 divided doses
- **The usual dose is then increased to** between 1000mg and 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems
- Your doctor may decide to lower your dose

Children and adolescents
Children and adolescents under 18 years of age:
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose.

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:
- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells
- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

Other serious side effects which need urgent medical attention:
- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath

Tell your doctor as soon as possible if you have any of the following side effects:
- Unusual behaviour including being very alert, and sometimes also aggressive, hyper-active and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days
- Hair, including body or facial hair, grows more than normal
- Temporary hair loss
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Bed wetting
- Weight gain

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male Fertility
Taking Depakote can be a contributing factor in male infertility.

Tell your doctor or pharmacist if any of the following side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.

Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Further Information

What Depakote 250mg Tablets contain
- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid)
- Hydrated colloidal silica, ,pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, sunset yellow aluminium lake (E110)

What Depakote 500mg Tablets contain
- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid)
- The other ingredients are: hydrated colloidal silica, pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, ponceau 4R aluminium lake (E124), indigo carmine aluminium lake (E132)

What Depakote looks like and contents of the pack
Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

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Manufacturer
Sanofi-aventis SA, Carretera C-35 (La Batlloria-Hostalric), Km 65.09
17404 Riells i Viabrea (Girona)

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 06/2011

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PAC 4

PACKAGE LEAFLET: INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

Valproic acid (as valproate semisodium)

SANOFI

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.
Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).
Depakote can be used when lithium can not be used.

2. Before you take Depakote

Do not take Depakote and tell your doctor if:
- x You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see Section 6: Further information)
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- x You have liver problems
- x You or a family member has ever had liver problems caused by taking a medicine
- x You have a rare illness called porphyria which affects your metabolism

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Take special care with Depakote
A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Check with your doctor or pharmacist before taking your medicine if:
- ▲ You are changing from another medicine that contains valproate
- ▲ The person taking this medicine is less than 18 years old
- ▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
- ▲ You have kidney problems
- ▲ You have problems with your pancreas
- ▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs
- ▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests)
- ▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain
Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:
- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:
- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Zidovudine - used for HIV infection
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Colestyramine - used for lowering blood cholesterol levels

Taking Depakote with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding
You should not take this medicine if you are pregnant or a woman of child-bearing age unless explicitly advised by your doctor.
Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Women who could become pregnant
Before you start taking Depakote, your doctor should discuss with you the possible problems when it is taken in pregnancy.
- Unplanned pregnancy is not desirable in women taking Depakote
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.**
  Depakote has no effect on how well the oral contraceptive pill works.
  Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Depakote if you become pregnant. Women taking Depakote during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time.
  These abnormalities include:
  - Head and face deformities including cleft palate (a gap or depression in the lip)
  - Deformities of the bones, including hip dislocation Malformations of the arms and legs

Turn Over

PAC 1

- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations with heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina bifida'
- Malformations of the urethra

Women who take Depakote during pregnancy may be more likely to have a baby with spina bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with spina bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.
Pregnant mothers who take Depakote may have babies with:

- blood clotting problems (such as blood not clotting or not clotting very well).This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar)
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).

Some babies born to mothers who took Depakote during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.
Talk to your doctor before you stop taking Depakote if you want to become pregnant. Do not stop taking Depakote suddenly, as it is likely that your illness will come back.

Women who are planning to get Pregnant
If you become pregnant, think you may be pregnant or plan to become pregnant while taking Depakote, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Breast-feeding
If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines
You may feel sleepy, confused or dizzy while taking this medicine.
If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote
Your medicine contains colours called **'sunset yellow aluminium lake (E110)'** and **'ponceau 4R aluminium lake (E124)'**. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure.

How to take your medicine

- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take
The normal dose is:

Adults including the elderly

- **Starting dose** is 750mg on the first day. This is usually taken as 2 or 3 divided doses
- **The usual dose is then increased to** between 1000mg and 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems

- Your doctor may decide to lower your dose

Children and adolescents
Children and adolescents under 18 years of age:
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose.

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:

- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells

- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.

Other serious side effects which need urgent medical attention:

- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes

Tell your doctor as soon as possible if you have any of the following side effects:

- Unusual behaviour including being very alert, and sometimes also aggressive, hyper-active and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days

- Hair, including body or facial hair, grows more than normal
- Temporary hair loss
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Bed wetting
- Weight gain
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male Fertility
Taking Depakote can be a contributing factor in male infertility.

Tell your doctor or pharmacist if any of the following side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.

Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Further Information

What Depakote 250mg Tablets contain

- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid)
- Hydrated colloidal silica, pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, sunset yellow aluminium lake (E110)

What Depakote 500mg Tablets contain

- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid)
- The other ingredients are: hydrated colloidal silica, pregelatinised starch, povidone, titanium dioxide (E171), talc; hypromellose phthalate, diacetylated monoglycerides, vanillin, ponceau 4R aluminium lake (E124), indigo carmine aluminium lake (E132)

What Depakote looks like and contents of the pack
Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS UK
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Fax: 01483 535432
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis SA, Carretera C-35 (La Batlloria-Hostalric), Km 65.09
17404 Riells i Viabrea (Girona)

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in November 2012

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.

Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Contents of the pack and other information

What Depakote 250mg Tablets contain
- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid)
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose , polyethylene glycol 6000, Methacrylic acid- ethyl acrylate copolymer (1:1), triethyl citrate, , vanillin, sunset yellow aluminium lake (E110).

What Depakote 500mg Tablets contain
- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid)
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose , polyethylene glycol 6000, Methacrylic acid- ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, ponceau 4R aluminium lake (E124), indigotine aluminium lake (E132)

What Depakote looks like and contents of the pack

Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.
Not all pack sizes may be marketed.

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This leaflet was last revised in Feburary 2015

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PACKAGE LEAFLET:
INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

Valproic acid (as valproate semisodium)

SANOFI

Is this leaflet hard to see or read?
Phone 0845 372 7101 for help

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING
Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.

Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.
Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).
Depakote can be used when lithium can not be used.

2. What you need to know before you take Depakote

Do not take Depakote
- x You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see Section 6: Contents of the pack and other information)
- x Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- x You have liver problems
- x You or a family member has ever had liver problems caused by taking a medicine
- x You have a rare illness called porphyria which affects your metabolism
- x If you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Warnings and precautions
A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor or pharmacist before taking Depakote if:
- ▲ You are changing from another medicine that contains valproate
- ▲ The person taking this medicine is less than 18 years old
- ▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
- ▲ You have kidney problems
- ▲ You have problems with your pancreas
- ▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs
- ▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests)
- ▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests
- ▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain
Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Other medicines and Depakote
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:
- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:
- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Zidovudine - used for HIV infection
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Colestyramine - used for lowering blood cholesterol levels

Taking Depakote with food and drink
Alcohol intake is not recommended during treatment.

Turn over

Pregnancy, breast feeding and fertility

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

FIRST PRESCRIPTION
If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY
If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY
If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your bipolar is controlled and the risks to your baby are reduced
- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT
Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.

Breast-feeding
If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines
You may feel sleepy, confused or dizzy while taking this medicine.
If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote
Your medicine contains colours called **'sunset yellow aluminium lake (E110)'** and **'ponceau 4R aluminium lake (E124)'**. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure. Depakote treatment must be started and supervised by a doctor specialised in the treatment of bipolar disorders.

How to take your medicine
- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take
The normal dose is:

Adults including the elderly
- **Starting dose** is 750mg on the first day. This is usually taken as 2 or 3 divided doses
- **The usual dose is then increased to** between 1000mg and 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems
- Your doctor may decide to lower your dose

Children and adolescents
Children and adolescents under 18 years of age:
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.
The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. Do not take a double dose to

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.
When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:
- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells
- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.

Other serious side effects which need urgent medical attention:
- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes

Tell your doctor as soon as possible if you have any of the following side effects:
- Unusual behaviour including being very alert, and sometimes also aggressive, hyper-active and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days
- Hair, including body or facial hair, grows more than normal
- Temporary hair loss
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Bed wetting
- Weight gain
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male Fertility
Taking Depakote can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes
- An increase in the number and severity of convulsions

Tell your doctor as soon as possible if you have any of the following side effects:
- Unusual behaviour including being very alert, and sometimes also aggressive, hyperactive and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:
- Swelling of gums or sore mouth
- Nail and nail bed disorders
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Temporary hair loss
- Hair disorders (changes in texture, colour or growth)
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Kidney disease
- Bed wetting
- Blood in the urine
- Weight gain
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)
- Obesity

Bone disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male fertility
Taking Depakote can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.
Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Depakote 250mg Tablets contain
- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid).
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose, polyethylene glycol 6000, Methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, sunset yellow aluminium lake (E110).

What Depakote 500mg Tablets contain
- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid).
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose, polyethylene glycol 6000, Methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, ponceau 4R aluminium lake (E124), indigotine aluminium lake (E132).

What Depakote Tablets look like and contents of the pack
- Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.
- Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
Fax: 01483 535432
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis SA, Carretera C-35 (La Batlloria-Hostalric), Km 65.09
17404 Riells i Viabrea (Girona), Spain

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in April 2018

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

valproic acid (as valproate semisodium)

SANOFI

Is this leaflet hard to see or read? Phone 0845 372 7101 for help.

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING

Depakote, valproate semisodium, can seriously harm an unborn child taken during pregnancy. If you are a female able to have a baby you must use an effective method of birth control (contraception) without interruption during your entire treatment with Depakote. Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or think you are pregnant.

Do not stop taking Depakote unless your doctor tells you to as your condition may become worse.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).

Depakote can be used when lithium cannot be used.

2. What you need to know before you take Depakote

Do not take Depakote and tell your doctor if:
X You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see section 6: Contents of the pack and other information).
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
X You have liver problems.
X You or a family member has ever had liver problems caused by taking a medicine.
X You have a rare illness called porphyria which affects your metabolism.
X You have a known metabolic disorder, i.e. a urea cycle disorder.
X You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
X You are pregnant (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).

If you are a woman able to have a baby you must not take Depakote unless you use an effective method of birth control (contraception) at all times during your treatment with Depakote. Do not stop taking Depakote or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Warnings and precautions
- A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking Depakote if:
▲ You are changing from another medicine that contains valproate.
▲ The person taking this medicine is less than 18 years old.
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have kidney problems.
▲ You have problems with your pancreas.
▲ You have a carnitine palmitoyltransferase type II deficiency.
▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs.
▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests).
▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests.
▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain
Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Other medicines and Depakote
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:
- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:
- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely.
- Medicines for depression.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.
- Zidovudine and protease inhibitors such as lopinavir and ritonavir – used for HIV infection.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine.
- Some medicines used for malaria such as mefloquine or chloroquine.
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide – used for cancer.
- Cimetidine – used for stomach ulcers.
- Cholestyramine – used for lowering blood cholesterol levels.
- Nimodipine.
- Propofol – used for anaesthesia.

Taking Depakote with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women
- You must not use Depakote if you are pregnant.
- If you are a woman able to have a baby, you must not take Depakote, unless you use an effective method of birth control (contraception) during your entire treatment with Depakote.
- Do not stop taking Depakote or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy
- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have bipolar disorder.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:
- **I AM STARTING TREATMENT WITH DEPAKOTE**
- **I AM TAKING DEPAKOTE AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING DEPAKOTE AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING DEPAKOTE**

I AM STARTING TREATMENT WITH DEPAKOTE
If this is the first time you have been prescribed Depakote your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with Depakote. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- Pregnancy must be excluded before start of treatment with Depakote with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Depakote.
- You must discuss the appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKOTE AND NOT PLANNING TO HAVE A BABY
If you are continuing treatment with Depakote but you don't plan to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Depakote. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with Depakote.
- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKOTE AND PLANNING TO HAVE A BABY
If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking Depakote or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of bipolar disorder so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of Depakote, switch you to another medicine, or stop treatment with Depakote a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking Depakote unless your doctor tells you to.
- Do not stop using your method of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with Depakote a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING DEPAKOTE
Do not stop taking Depakote, unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of bipolar disorder so that alternative treatment options can be evaluated. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking Depakote unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of bipolar disorder to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Depakote during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines
You may feel sleepy, confused or dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote
Your medicine contains colours called 'sunset yellow aluminium lake (E110)' and 'ponceau 4R aluminium lake (E124)'. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure.

Depakote treatment must be started and supervised by a doctor specialised in the treatment of bipolar disorders.

How to take your medicine
- Take this medicine by mouth.
- Swallow the tablets whole with a drink of water. **Do not** crush or chew them.
- This medicine can be taken with or after a meal.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.

How much to take
The normal dose is:

Adults including the elderly
- **Starting dose is 750mg on the first day. This is usually taken as 2 or 3 divided doses.**
- **The usual dose is then increased to** between 1000mg and 2000mg each day.
- Your doctor may decide to increase your dose depending on your illness.

If you have kidney problems
- Your doctor may decide to lower your dose.

Children and adolescents under 18 years of age
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania.

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:
- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells:
- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.

Other serious side effects which need urgent medical attention:
- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)

- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes
- An increase in the number and severity of convulsions

Tell your doctor as soon as possible if you have any of the following side effects:
- Unusual behaviour including being very alert, and sometimes also aggressive, hyperactive and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:
- Swelling of gums or sore mouth
- Nail and nail bed disorders
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Temporary hair loss
- Hair disorders (changes in texture, colour or growth)
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Kidney disease
- Bed wetting
- Blood in the urine
- Weight gain
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)
- Obesity

Bone disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Tests
Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male fertility
Taking Depakote can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.
Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Depakote 250mg Tablets contain
- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid).
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose, polyethylene glycol 6000, Methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, sunset yellow aluminium lake (E110).

What Depakote 500mg Tablets contain
- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid).
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose, polyethylene glycol 6000, Methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, ponceau 4R aluminium lake (E124), indigotine aluminium lake (E132).

What Depakote Tablets look like and contents of the pack
- Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.
- Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
Fax: 01483 535432
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis SA, Carretera C-35 (La Batlloria-Hostalric), Km 65.09
17404 Riells i Viabrea (Girona), Spain

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in August 2018

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

valproic acid (as valproate semisodium)

SANOFI

Is this leaflet hard to see or read? Phone 0845 372 7101 for help.

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING

Depakote, valproate semisodium, can seriously harm an unborn child taken during pregnancy. If you are a female able to have a baby you must use an effective method of birth control (contraception) without interruption during your entire treatment with Depakote. Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or think you are pregnant.

Do not stop taking Depakote unless your doctor tells you to as your condition may become worse.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg Tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).

Depakote can be used when lithium cannot be used.

2. What you need to know before you take Depakote

Do not take Depakote and tell your doctor if:
X You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see section 6: Contents of the pack and other information).
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
X You have liver problems.
X You or a family member has ever had liver problems caused by taking a medicine.
X You have a rare illness called porphyria which affects your metabolism.
X You have a known metabolic disorder, i.e. a urea cycle disorder.
X You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome).
X You are pregnant (see 'Pregnancy, breast-feeding and fertility – Important advice for women' below).

If you are a woman able to have a baby you must not take Depakote unless you use an effective method of birth control (contraception) at all times during your treatment with Depakote. Do not stop taking Depakote or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Warnings and precautions
- A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking Depakote if:
▲ You are changing from another medicine that contains valproate.
▲ The person taking this medicine is less than 18 years old.
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have kidney problems.
▲ You have problems with your pancreas.
▲ You have a carnitine palmitoyltransferase type II deficiency.
▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs.
▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests).
▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests.
▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain
Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Other medicines and Depakote
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:
- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:
- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely.
- Medicines for depression.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.
- Zidovudine and protease inhibitors such as lopinavir and ritonavir – used for HIV infection.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine.
- Some medicines used for malaria such as mefloquine or chloroquine.
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide – used for cancer.
- Cimetidine – used for stomach ulcers.
- Cholestyramine – used for lowering blood cholesterol levels.
- Nimodipine.
- Propofol – used for anaesthesia.
- Oestrogen-containing products (including some birth control pills).

Taking Depakote with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women
- You must not use Depakote if you are pregnant.
- If you are a woman able to have a baby, you must not take Depakote, unless you use an effective method of birth control (contraception) during your entire treatment with Depakote.
- Do not stop taking Depakote or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy
- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have bipolar disorder.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:
- **I AM STARTING TREATMENT WITH DEPAKOTE**
- **I AM TAKING DEPAKOTE AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING DEPAKOTE AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING DEPAKOTE**

I AM STARTING TREATMENT WITH DEPAKOTE
If this is the first time you have been prescribed Depakote your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with Depakote. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- Pregnancy must be excluded before start of treatment with Depakote with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Depakote.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKOTE AND NOT PLANNING TO HAVE A BABY
If you are continuing treatment with Depakote but you don't plan to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Depakote. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with Depakote.
- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKOTE AND PLANNING TO HAVE A BABY
If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking Depakote or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of bipolar disorder so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of Depakote, switch you to another medicine, or stop treatment with Depakote a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking Depakote unless your doctor tells you to.
- Do not stop using your method of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with Depakote a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING DEPAKOTE
Do not stop taking Depakote, unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of bipolar disorder so that alternative treatment options can be evaluated. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking Depakote unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of bipolar disorder to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Depakote during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:
- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding
If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines
You may feel sleepy, confused or dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote
Your medicine contains colours called 'sunset yellow aluminium lake (E110)' and 'ponceau 4R aluminium lake (E124)'. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure.

Depakote treatment must be started and supervised by a doctor specialised in the treatment of bipolar disorders.

How to take your medicine
- Take this medicine by mouth.
- Swallow the tablets whole with a drink of water. **Do not** crush or chew them.
- This medicine can be taken with or after a meal.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.

How much to take
The normal dose is:

Adults including the elderly
- **Starting dose is 750mg on the first day. This is usually taken as 2 or 3 divided doses.**
- **The usual dose is then increased to** between 1000mg and 2000mg each day.
- Your doctor may decide to increase your dose depending on your illness.

If you have kidney problems
- Your doctor may decide to lower your dose.

Children and adolescents under 18 years of age
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania.

Tests
Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should
If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote
If you forget to take a dose at the right time, take it as soon as you remember. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Depakote
Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions
If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:
- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells:
- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.

Other serious side effects which need urgent medical attention:
- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)

1 Name of the medicinal product

Depakote 250mg Tablets.
Depakote 500mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

Containing 538.20mg of valproate semisodium* per tablet (equivalent to 500mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

3 Pharmaceutical form

Gastro-resistant tablets.

4 Clinical particulars

4.1 Therapeutic indications

Depakote is indicated for the acute treatment of a manic episode associated with bipolar disorder.

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

There is no clear correlation between daily dose, plasma concentration and therapeutic effect. Optimum dosage should be determined mainly by clinical response. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected.

In mania it is generally agreed that plasma levels around 45 to 50μg/ml are needed to allow efficacy; most patients receiving Depakote during controlled clinical trials achieved a maximum plasma concentration of greater than 75μg/ml.

Dosage

Adults
The recommended initial dose is 750mg daily in 2 to 3 divided doses. From day 2 the dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses usually range between 1000 and 2000mg (i.e. 20 – 30 mg/kg/day body weight). Where adequate control is not achieved within this range the dose may be increased.
Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.

When using Depakote with other psycotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)
Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.
Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.
Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote

should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of child-bearing potential should not be started on Depakote without specialist psychiatric advice. Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effects of Depakote on other drugs

- Clozapine, haloperidol, lithium
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

- Antipsychotics , MAO inhibitors, antidepressants and benzodiazepines
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Depakote might increase the risk of rash.

- ***Zidovudine***
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy. On the other hand, combination of ***felbamate*** and Depakote may increase valproic acid plasma concentration. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem***, *imipenem* and *meropenem*: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when panipenem, imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood level is recommended.

Colestyramine may decrease the absorption of Depakote.

4.5.3 Other interactions

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Use during pregnancy and lactation

Women of child-bearing potential should not be started on Depakote without specialist psychiatric advice.
Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).
Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.
If pregnancy is planned, consideration should be given to cessation of Depakote treatment, if appropriate.
When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.
Epidemiological studies have suggested an association between in-utero exposure to Depakote and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.
Notwithstanding those potential risks, no sudden discontinuation in the bipolar therapy should be undertaken as this may lead to an immediate relapse of the underlying symptoms.

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of Depakote during pregnancy has been described as follows:

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.
There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers treated with valproate.
Some data from studies, of women with epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

- In view of the above data
When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of childbearing age should be informed of the risks and benefits of continuing treatment throughout pregnancy.
Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.
Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.
Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical

effects. There appears to be no contra-indication to breast feeding by patients on Depakote.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, but they are

usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.
Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: cutaneous reactions such as exanthematous rash rarely occur with Depakote. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose symptoms, emergency procedures, antidotes

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.
Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.
Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 Pharmaceutical particulars

6.1 List of Excipients

Depakote 250 mg: Colloidal silica, hydrated; starch pregelatinised; povidone; titanium dioxide (E171); talc; hypromellose phthalate; diacetylated monoglycerides; sunset yellow aluminium lake (E110); vanillin.

Depakote 500 mg: Colloidal silica, hydrated; starch pregelatinised; povidone; titanium dioxide (E171); talc; hypromellose phthalate; diacetylated monoglycerides; ponceau 4R aluminium lake (E124); indigo carmine aluminium lake (E132); vanillin.

6.2 Major incompatibilities

Not relevant.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 90 tablets.

6.6 Special precautions for disposal

None.

7 Marketing authorisation holder

Sanofi-Synthelabo Limited
One Onslow Street
Guildford
Surrey
GU1 4YS

8 Marketing authorisation number

Depakote 250 mg: 11723/0251
Depakote 500 mg: 11723/0252

9 Date of the first authorisation or renewal

21 December 2000

10 Date of revision of the text

September 2005

11 Legal classification

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Depakote 250mg Tablets.
Depakote 500mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

Containing 538.20mg of valproate semisodium* per tablet (equivalent to 500mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 Pharmaceutical form

250mg: Oval, orange gastro-resistant tablets.
500mg: Oval, lilac pink gastro-resistant tablets

4 Clinical particulars

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in

clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy
When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.

When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)
Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,
These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Women of childbearing potential: This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment (see also section 4.6 Pregnancy and Lactation).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- ***Clozapine, haloperidol, lithium***
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

- ***Antipsychotics , MAO inhibitors, antidepressants and benzodiazepines***
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Phenobarbital***
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
The risk of rash associated with the use of Depakote may be increased if lamotrigine is also administered. Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy. On the other hand, combination of ***felbamate*** and Depakote may increase valproic acid plasma concentration. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem***, *imipenem* and *meropenem*: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when panipenem, imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood level is recommended.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Pregnancy and lactation

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment.

Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).

Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.

If pregnancy is planned, consideration should be given to cessation of Depakote treatment.

When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- Risk associated with bipolar therapy
This drug should be withdrawn under specialist supervision.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Depakote is prescribed for the first time or a woman already treated with Depakote is planning a pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including red cell aplasia.
Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: Rash rarely occurs with Depakote. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic, ATC code: N03AG01
Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 Pharmaceutical particulars

6.1 List of excipients

Depakote 250mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Sunset yellow aluminium lake (E110), Vanillin.

Depakote 500mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Ponceau 4R aluminium lake (E124), Indigo carmine aluminium lake (E132), Vanillin.

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 90 tablets.

6.6 Special precautions for disposal

No special requirements

7 Marketing authorisation holder

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 Marketing authorisation holder

Depakote 250 mg: 04425/0199
Depakote 500 mg: 04425/0200

9 Date of the first authorisation or renewal

Date of first authorisation:
Depakote 250mg and 500mg: 4 February 2009

Date of latest renewal:
Depakote 250mg: 1 June 2009
Depakote 500mg: 24 March 2009

10 Date of revision of the text

12 November 2010

Legal status

POM

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Depakote 250mg Tablets.
Depakote 500mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

Containing 538.20mg of valproate semisodium* per tablet (equivalent to 500mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 Pharmaceutical form

250mg: Oval, orange gastro-resistant tablets.
500mg: Oval, lilac pink gastro-resistant tablets

4 Clinical particulars

4.1 Therapeutic indications

Depakote is indicated for the acute treatment of a manic episode associated with bipolar disorder.

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

There is no clear correlation between daily dose, plasma concentration and therapeutic effect. Optimum dosage should be determined mainly by clinical response. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected.

In mania it is generally agreed that plasma levels around 45 to 50µg/ml are needed to allow efficacy; most patients receiving Depakote during controlled

clinical trials achieved a maximum plasma concentration of greater than 75µg/ml.

Dosage

Adults
The recommended initial dose is 750mg daily in 2 to 3 divided doses. From day 2 the dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. Daily doses usually range between 1000 and 2000mg (i.e. 20 – 30 mg/kg/day body weight). Where adequate control is not achieved within this range the dose may be increased.

Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.

Elderly
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

Children and adolescents
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Depakote since they employ the same metabolic pathway (see also sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special Warnings and Precautions for Use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Depakote, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

Combined Therapy

When starting Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in

combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.

When using Depakote with other psycotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)

Optimum dosage is mainly determined by control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient's condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

4.4.1 Special Warnings

Liver dysfunction:

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):
- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures,

These are an indication for immediate withdrawal of the drug. Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk

decreases with increasing age. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

Women of childbearing potential (see section 4.6): A decision to use Depakote in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Depakote is prescribed for the first time as well as before a woman already treated with valproate semisodium is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation).

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8. Undesirable Effects).

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Depakote, the potential benefit of Depakote should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Depakote.

Weight gain: Depakote very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain

at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of child-bearing potential should not be started on Depakote without specialist psychiatric advice. Adequate counselling should be made available to all pregnant women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Depakote is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Depakote on other drugs

- Clozapine, haloperidol, lithium
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

- Antipsychotics , MAO inhibitors, antidepressants and benzodiazepines
Depakote may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone
Depakote increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin
Depakote decreases phenytoin total plasma concentration. Moreover Depakote increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine
Clinical toxicity has been reported when Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine
The risk of rash associated with the use of Depakote may be increased if lamotrigine is also administered. Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate.

- Zidovudine
Depakote may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- Vitamin K-dependent anticoagulants
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- Temozolomide
Co-administration of temozolomide and Depakote may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Depakote

Antiepileptics with enzyme inducing effects (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy. On the other hand, combination of ***felbamate*** and Depakote may increase valproic acid plasma concentration. Depakote dosage should be monitored.

Mefloquine and ***Chloroquine*** increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

Carbapenem antibiotics such as ***panipenem***, *imipenem* and *meropenem*: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when panipenem, imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood level is recommended.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Depakote usually has no enzyme inducing effect; as a consequence, Depakote does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Pregnancy and lactation

Women of child-bearing potential should not be started on Depakote without specialist psychiatric advice.

Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).

Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.

If pregnancy is planned, consideration should be given to cessation of Depakote treatment, if appropriate.

When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- Risk associated with bipolar therapy
As a measure of precaution, immediate discontinuation should be avoided, as it is not clear if this may lead to rapid relapse of bipolar symptoms.
Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data
When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Depakote is prescribed for the first time or a woman already treated with Depakote is planning a pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2 Lactation

Excretion of Depakote in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects

The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

Congenital and familial/genetic disorders: (see section 4.6. Pregnancy and Lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Special Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1 Special Warnings).

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special Warnings and Precautions for Use).

Nervous system disorders: Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2. Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Bone marrow failure, including red cell aplasia.
Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and Lactation).

Skin and subcutaneous tissue disorders: Rash rarely occurs with Depakote. In very rare cases, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders: the occurrence of vasculitis has occasionally been reported.

Ear disorders: hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported

General disorders: very rare cases of non severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression, or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic, ATC code: N03AG01
Depakote exerts its effects mainly on the central nervous system.

The most likely mode of action for Depakote is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.

Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases T_{max} by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from β-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 Pharmaceutical particulars

6.1 List of excipients

Depakote 250mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Sunset yellow aluminium lake (E110), Vanillin.

Depakote 500mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Ponceau 4R aluminium lake (E124), Indigo carmine aluminium lake (E132), Vanillin.

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Aluminium/aluminium blister packs containing 90 tablets.

6.6 Special precautions for disposal

No special requirements

7 Marketing authorisation holder

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 Marketing authorisation holder

Depakote 250 mg: 04425/0199

Depakote 500 mg: 04425/0200

9 Date of the first authorisation or renewal

Date of first authorisation:
Depakote 250mg and 500mg: 4 February 2009

Date of latest renewal:
Depakote 250mg: 1 June 2009
Depakote 500mg: 24 March 2009

10 Date of revision of the text

16 September 2010

Legal status

POM