Annex F: Sodium valproate Supporting Information

Contents

1 Sodium valproate

Pharmacology

1. Valproic acid is also known as dipropylacetic acid (DPA), 2-propyl-pentanoic acid, or 2-propylvaleric acid. There are two salts of valproic acid which are used therapeutically, of which the sodium salt (sodium valproate) is more commonly used than the magnesium salt (magnesium valproate) which is marketed in South and Central America.1 A stable compound of sodium valproate and valproic acid containing a 1:1 molar amount of each is known as divalproex sodium, or valproate semisodium.

2. Some examples of these variants are below. Modified forms such as prolonged release and gastro-resistant forms are also available.

    - Sodium valproate – Epilim, Episenta
    - Valproic acid – Convulex
    - Divalproex sodium / Valproate semisodium – Belvo, Depakote, Epival
    - Other combination of sodium valproate and valproic acid - Epilim Chrono

3. The exact mechanism of action for sodium valproate in management of seizures, psychiatric treatment, and migraine prophylaxis is not completely understood.[2]

History

4. Valproic acid was first synthesised in 1882 by Burton, and was used as a laboratory solvent. The discovery of its anticonvulsant properties was accidental; used as a solvent in testing other potential anticonvulsants, the scientists Eymard, Meunier and Meunier found that the valproic acid itself had an anticonvulsant effect. They presented these findings at a meeting in 1962, and published their findings the following year.[3] A French patent was obtained by Berthier laboratories in 1969.

[1] Simon, D and Penry, JK. Sodium Di-*N*-Propylacetate (DPA) in the Treatment of Epilepsy: A Review. Epilepsia 1975: 16: 549-573. doi: 10.1111/j.1528-1157.1975.tb04738.x
[2] https://www.drugbank.ca/drugs/DB00313
[3] 'The discovery of valproate' In Löscher, W. Valproate. Birkhäuser Basel doi: 10.1007/978-3-0348-8759-5_1

Following successful animal trials, a research group led by Carraz carried out the first clinical trials in patients with epilepsy, which was published in 1964.[4]

5. Sodium valproate was initially licensed in France in 1967, with the approved indications of generalised or focalised epilepsies, and personality or character disorders linked to epilepsy. Between 1969 and 1973, sodium valproate supply commenced in Belgium, Holland, Luxembourg, West Germany and Spain, through a licensing agreement with the Belgian company Labaz.[5] The introduction of sodium valproate to the stable of available treatments for epilepsy was greatly welcomed.[6]

Licensing in the UK

The application for sodium valproate was received by the marketing authority at the time, the Department for Health and Social Security (DHSS) in 1971, and considered by the Committee of Safety of Medicines (CSM). In January 1972, the CSM Sub-Committee on Toxicity and Clinical Trials reported that clinical studies of sodium valproate did not show adequate evidence of safety and efficacy, and further toxicological and teratological data was required. After requesting further clinical data, in May the same year, they concluded that they were unable to advise granting the licence, due to inadequate data on toxicology and teratology. Specifically they raised concerns about this data "*in view of the expected long term administration of the drug*". However, by the following month the same Sub-Committee reported that they had received sufficient data to grant a conditional license for a year, limiting sodium valproate use to hospitals and other specialist centres for epilepsy, provided all patients were monitored for therapeutic efficacy and safety, and the results reported to the licensing authority.[7]

6. A full clinical trial was not carried out in the UK,[8] and contemporary accounts draw attention to the unusual nature of the decision taken to consider available data from

[4] i*bid.*
[5] Sanofi written evidence to the Review
[6] One clinician described sodium valproate as "*having been greeted by some as the greatest thing since Greta Garbo*".[6] (Addy, DP. Childhood epilepsy. BMJ 1978:2(6140): 811-812 doi: 10.1136/bmj.2.6140.811)
[7] MHRA written evidence to the Review – Minutes of the CSM January, May and June 1972, and CPS January 1972
[8] MHRA written evidence to the Review - MC 76/112A 'A Note on Epilim – Sodium Valproate' 1976

France instead.[9] Moreover, a subsequent note by the Medicines Commission draws attention to this data being collected from a patient sample which differed from the majority of patients in the UK "*in its genetic composition, dietary intake, and other drugs administered concomitantly.*"[10]

7. An application for a full product licence was submitted in September 1973 along with data from animal studies.[11] This was considered by DHSS, and after discussion of conditions of licencing with Reckitt-Labaz, a full product licence was granted in October 1974, backdated to August 1973.[12]

8. Valproate, in the form of valproic acid or semisodium valproate, was licensed for use in 2001 for the treatment of manic episodes associated with bipolar disorder.

'Off-label' use of sodium valproate

Psychiatric indications

9. In addition to the licensed use of semisodium valproate for acute manic episodes, it has been used for other psychiatric indications including: augmentation of antidepressant drug treatment and prophylaxis to reduce episodes of bipolar or unipolar disorder.[13] The most recent Cochrane Reviews on the use of sodium valproate state:

    - Acute mania (licensed use): valproate is an effective antimaniac treatment[14]
    - Maintenance treatment of bipolar disorder: There is limited evidence which supports the efficacy of valproate in the long-term treatment of bipolar disorder. Clinicians and patients should consider the acceptability and

[9] Reported in: US Department of Health, Education and Welfare. Workshop on Antiepileptic Drug Development, April 15 1977, Arlington, Virginia.
[10] MHRA written evidence to the Review - MC 76/112A 'A Note on Epilim – Sodium Valproate' 1976
[11] Sanofi written evidence to the Review
[12] MHRA written evidence to the Review – Minutes of the CSM, March and September 1973
[13] RCPsych 'Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness' 2018
[14] Jochim, J et al. Valproate for acute mania. Cochrane Systematic Review - Intervention 07 October 2019 doi: 10.1002/14651858.CD004052.pub2

tolerability profile when choosing between lithium and valproate as long-term treatment for bipolar disorder.[15]

- Schizophrenia: there is limited evidence (from open randomised control trials) that the augmentation of antipsychotics with valproate may be effective for overall clinical response, and for managing excitement and aggression. Valproate was associated with a number of adverse events. Further randomised blinded studies are necessary before any clear recommendation can be made.[16]

- Aggression: Insufficient evidence on the efficacy of antiepileptic drugs in reducing aggression was found to draw a firm conclusion.[17]

- Alcohol dependence: There is insufficient good quality evidence to support the clinical use of anticonvulsants to treat alcohol dependence.[18]

- Agitation in dementia: Valproate preparations are probably ineffective in treating agitation in people with dementia, and are associated with a higher rate of adverse effects. Valproate therapy cannot be recommended for this use.[19]

Migraine prophylaxis

10. Sodium valproate has also been used in the UK for migraine prophylaxis. The 'off-label' use of sodium valproate for migraine was first included in the BNF in 2001. Early small-scale studies demonstrated that sodium valproate was effective in migraine

[15] Cipriani, A et al. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder Cochrane Systematic Review - Intervention 17 October 2013 doi: 10.1002/14651858.CD003196.pub2
[16] Wang, Y et al. Valproate for schizophrenia. Cochrane Systematic Review - Intervention 24 November 2016 doi: 10.1002/14651858.CD004028.pub4
[17] Huband, N et al. Antiepileptics for aggression and associated impulsivity. Cochrane Systematic Review - Intervention 17 February 2010 doi: 10.1002/14651858.CD003499.pub3
[18] Pani, PP et al. Anticonvulsants for alcohol dependence. Cochrane Systematic Review - Intervention 13 February 2014 doi: 10.1002/14651858.CD008544.pub2
[19] Baillon, SF et al. Valproate preparations for agitation in dementia. Cochrane Systematic Review - Intervention 05 October 2018 doi: 10.1002/14651858.CD003945.pub4

prophylaxis.[20] This was confirmed in subsequent reviews,[21] including professional guidelines[22] and a Cochrane Review.[23] 2010 guidelines by the British Association for the Study of Headache (BASH) state that the evidence-base for efficacy is good for valproate as a first-line prophylactic drug against migraine. It recommends beta-blockers as first line, and sodium valproate/topiramate as second-line, noting their contraindication during pregnancy. It does not recommend sodium valproate for cluster headache.[24]

Neuropathic pain

11. The BNF suggested the use of sodium valproate in management of neuropathic pain from 1998 – 2005, but has not done so since. Early studies on the efficacy of valproate in pain management were contradictory. A small study of 20 patients found some improvement[25], and a subsequent study with three parallel group trials found high efficacy in one group, and no improvement above a placebo in the others. [26] An update published in 2010 reported that the evidence for efficacy of valproate in pain management remained inconsistent.[27]

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[20] *For example*: Sørensen, KV. Valproate: a new drug in migraine prophylaxis. Acta Neurologica Scandinavica 1988: 78(4): 346-348 doi: 10.1111/j.1600-0404.1988.tb03667.x; Hering, R and Kuritzky, A. Sodium Valproate in The Prophylactic Treatment of Migraine: A Double Blind Study Versus Placebo. Cephalalgia 1992: 12(2): 81-84 doi: 10.1046/j.1468-2982.1992.1202081.x; Jensen, R et al. Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Neurology 1994: 44(4): 647-647 doi: 10.1212/wnl.44.4.647

[21] *For example*: Rothrock, JF. Clinical Studies of Valproate for Migraine Prophylaxis. Cephalalgia 1997: 17(2): 81-83 doi: 10.1046/j.1468-2982.1997.1702081.x; Managing migraine. Drug and Therapeutics Bulletin 36(6) June 1998

[22] Silberstein, SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology 2000: 55(6): 754-762 doi: 10.1212/wnl.55.6.754;

[23] Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004; Issue 3. Article CD003226. doi: 10.1002/14651858.CD003226.pub2.

[24] British Association for the Study of Headache **(**BASH). Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache, Medication-Overuse Headache. 3rd edition (1st revision) 2010. Available online here.

[25] Peiris, JB et al. Sodium valproate in trigeminal neuralgia. Medical Journal of Australia 1980: 2(5): 278 doi: 10.5694/j.1326-5377.1972.tb47277.x

[26] Finnerup, NB et al. Algorithm for neuropathic pain treatment: An evidence based proposal. PAIN 2005: 118(3): 289-305 doi: 10.1016/j.pain.2005.08.013

[27] Finnerup, NB et al. The evidence for pharmacological treatment of neuropathic pain. PAIN 2010: 150(3): 573-581 doi: 10.1016/j.pain.2010.06.019

12. A consensus meeting of the International Association for the Study of Pain (IASP) suggested that valproic acid should only be considered as a third-line medication.[28] A Cochrane Review in 2011 concluded that there was "*too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies. There is insufficient evidence to support the use of valproic acid or sodium valproate as a first-line treatment for neuropathic pain.*"[29] In the same year, a NICE consultation on neuropathic pain found that evidence on the efficacy of sodium valproate was insufficient.[30] Sodium valproate does continue to form part of neuropathic pain protocols in specialist settings, with due warnings about the Pregnancy Prevention Programme.[31]

Prevalence of valproate use in the UK

13. Carbamazepine and valproates were among the most commonly used medications for epilepsy in the UK throughout 1993–2008.[32] During this period, use of phenytoin and barbiturates decreased, and lamotrigine and levetiracetam increased. Newer AEDs were more frequently prescribed to younger participants, especially women aged 15–44 years, while older adults were more likely to be prescribed longer established AEDs.[33] Between 1996 and 2016, prescribing of lamotrigine and levetiracetam continued to increase in the UK and Ireland, and valproate and carbamazepine use declined.[34]

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[28] Dworkin, RH et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. PAIN 2007: 132(3): 237-251 doi: 10.1016/j.pain.2007.08.033

[29] Gill, D et al. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2011: 10 doi: 10.1002/14651858.CD009183.pub2

[30] NICE. Neuropathic pain: The pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline Draft for consultation, September 2011. Available online here.

[31]For example see resources from Salford Royal https://www.srft.nhs.uk/EasysiteWeb/getresource.axd?AssetID=17102&type=full&servicetype=Inline, and South & West Devon Formulary and Referral https://southwest.devonformularyguidance.nhs.uk/formulary/chapters/4.-central-nervous-system/neuropathic-pain

[32] Nicholas, J. M., et al. (2012). "Trends in antiepileptic drug utilisation in UK primary care 1993–2008: Cohort study using the General Practice Research Database." Seizure **21**(6): 466-470; Man, S.-L., et al. (2012). "Antiepileptic Drugs during Pregnancy in Primary Care: A UK Population Based Study." PLoS One **7**(12): e52339.

[33] i*bid.*

[34] Kinney, M. O., et al. (2018). "Changing antiepilepsy drug-prescribing trends in women with epilepsy in the UK and Ireland and the impact on major congenital malformations." Journal of Neurology, Neurosurgery

14. Data provided by Sanofi (manufacturers of Epilim and Depakote) and current to August 2018 suggest that valproate use has continued to decline (for both valproate and bipolar disorder). The share of all valproate-based medicines in the epilepsy market has reduced over the past 5 years from 12.1% to 9.1%. The number of women of childbearing potential taking Epilim has reduced from 17,172 to 15,633, and female children from 3,271 to 2,068 in the same period.[35]

15. An audit published in 2018 found that amongst those treated for bipolar disorder at 55 mental health Trusts in the UK, 24% of women aged younger than 50 years were prescribed valproate-containing medicines.[36] The Royal College of Psychiatrists stated that the prevalence of off-label use for other psychiatric treatments is unknown but estimates from other countries range between 14 – 35%.[37] Data provided by Sanofi show that the Depakote share of the bipolar market has declined from 4.1% to 3.5%. The number of women of childbearing potential taking Depakote has reduced by 38.8% from 8,177 to 5,002 over this period[38].

16. These figures are supported by data from the Clinical Practice Research Datalink, which suggested that approximately 35,000 women per year aged 14 to 45 had a prescription for sodium valproate between 2010 and 2012, the majority for epilepsy. Of these, at least 375 per year had a prescription for sodium valproate while pregnant.[39]

17. NHS prescribing data for sodium valproate (including valproic acid and semisodium valproate) for the period January - March 2018 and October – December 2019 continues to show a reduction in valproate prescribing in female patients 45 years and under.[40]

& Psychiatry **89**(12): 1320.; Pickrell, W. O., et al. (2014). "Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010." Seizure **23**(1): 77-80.; Man, S.-L., et al. (2012). "Antiepileptic Drugs during Pregnancy in Primary Care: A UK Population Based Study." PLoS One **7**(12): e52339.

[35] Sanofi written evidence to the Review

[36] Paton, C et al. A UK clinical audit addressing the quality of prescribing of sodium valproate for bipolar disorder in women of childbearing age. BMJ Open 2018: 8(4) doi: 10.1136/bmjopen-2017-020450

[37] Royal College of Psychiatrists written evidence to the Review

[38] Sanofi written evidence to the Review

[39] Medicines related to valproate: risk of abnormal pregnancy outcomes. Drug Safety Update 8(6) January 2015

[40] Prescribing for Sodium Valproate. NHS BSA Prescription Data. https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/sodium-valproate

Prevalence of valproate use internationally

18. Global prescribing practices vary. For example, one study found that in many countries, sodium valproate is the most frequently prescribed AED[41]. In contrast, a recent study in the US found only 1.1% of patients were on valproate monotherapy and polytherapy in the period 2012-2016.[42] However, there is a trend towards declining use of valproic acid and carbamazepine, and increase in new-generation AEDs such as lamotrigine (Europe[43]), particularly linked with the EMA regulatory procedures and use in female patients of childbearing potential (Lithuania[44], Finland[45], and France[46]).

[41] Egunsola, O., et al. (2017). "Anti-epileptic drug utilisation in paediatrics: a systematic review." BMJ paediatrics open **1**(1): e000088-e000088.
[42] Meador, K. J., et al. (2018). "Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy." Epilepsy & Behavior 84: 10-14.
[43] Tomson, T., et al. (2019). "Declining malformation rates with changed antiepileptic drug prescribing." Neurology **93**(9): e831.
[44] Puteikis, K., et al. (2019). "Valproate utilisation trends among girls and women from 2013 to 2018." Seizure **70**: 77-81.
[45] Virta, L. J., et al. (2018). "Declining trend in valproate use in Finland among females of childbearing age in 2012–2016 – a nationwide registry-based outpatient study." European Journal of Neurology **25**(6): 869-874.
[46] Degremont, A., et al. (2018). "Impact of the French Agency for the Safety of Medicines and Health Products communication on sodium valproate prescription in women of childbearing potential age." Revue d'Épidémiologie et de Santé Publique **66**: S426-S427.

2 Estimates of numbers affected by in-utero exposure to sodium valproate

Estimates in the UK

19. There has been no official estimate of the number of children exposed to sodium valproate in utero since it was licensed in 1973, and information has not been collected centrally.[47] A number of estimates have been shared with the review, which are summarised below:

Table F.1 *Estimates of numbers affected by valproate exposure in utero*

Source	Assumptions	Estimate
INFACT[48]	• Using Summary of Live Birth Statistics from the Office of National Statistics (ONS) for England and Wales from 1996-2011 and Man et al (2012)[49]. • Using estimate of 40% with cognitive and minor physical effects, and 10% with major congenital malformations • Projected to period 1973-2011	**1973-2011** • 33,798 exposed • 13,510 – 20,000 significantly affected
FACSaware[50]	• Using estimate from Man et al[51] • Estimate pregnancies in 2009, and extrapolated to period 1994 – 2013 • Estimate 35-40% significant physical or cognitive effect	**1994 – 2013** • 24,000 exposed • 9,600 affected by significant physical or cognitive effect

[47] Hansard 9th March 2019. Pregnancy: Sodium Valproate. Written question 131831. Link here.
[48] INFACT written evidence to the Review
[49] Man et al. Antiepileptic Drugs during Pregnancy in Primary Care: A UK Population Based Study. PLOS ONE 2012: **7**, e52339
[50] FACSAware written evidence to the Review.
[51] Man et al. (2012) as above.

Bromley, Clayton-Smith and Turnpenny[52]	• 'Back of the envelope calculation' using women taking valproate and birth rate	• 20,000[53] affected (to date, both neurodevelopmental and physical effects)

20. The figure of 20,000 appears to be the most often quoted, appearing in articles in the media,[54] and Parliament.[55] INFACT use this figure in calculating the resource required by individuals affected by valproate between 1973 and 2013 to total £181 billion.[56]

Estimates in Ireland

21. The group OACS Ireland used UK and international data, to estimate that there have been approximately 30 valproate pregnancies per year, or over 1,000 since 1983. Using the figures for risk above, this would equate to over 100 children with physical malformations, and approximately 400 with some form of neurodevelopmental delay.[57]

22. Health Service Executive Ireland formalised this estimate, using a number of data sources to estimate the prevalence of major congenital abnormalities and neurodevelopmental disorders arising from exposure of children to sodium valproate in the womb, between 1975 and 2015. This estimated that in this period, approximately 3,126 babies were exposed to valproate in utero. Using international data on the rates of congenital malformation and neurodevelopmental delay, they estimate that in this period, between 153 and 341 children will have a major

[52] OH Dr Bromley, Professor Clayton-Smith and Professor Turnpenny 26th November 2018
[53] *This figure is also quoted in:* J. Clayton-Smith *et al.*, Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability. Orphanet Journal of Rare Diseases 2019: **14**, 180.
[54] *For example, see*: S Boseley 'Birth defect risks of sodium valproate 'known 40 years ago'' The Guardian 26th September 2017; Z Adesina 'Disabilities caused in babies by epilepsy drug a 'scandal'' BBC Inside Out 22nd January 2018; S Petkar 'PREGNANCY RISKS: What is sodium valproate, what are the side effects and what is foetal valproate syndrome? The Sun 22nd January 2018; K Lay 'Birth defects from epilepsy drug sodium valproate could last generations' The Times 23rd January 2018.
[55] Hansard 19th October 2017. Valproate and Foetal Anticonvulsant Syndrome. Vol 629 Col 1065 http://bit.ly/2EilvGw
[56] INFACT written evidence to the Review
[57] OACS Ireland written evidence to the Review

congenital malformation, and up to 1,250 will have some form of neurodevelopmental delay.[58]

Estimates in France

23. A study carried out by the French agency ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and CNAMTS (Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés) estimated the number of children exposed to valproate in utero in the period 1967 – 2016, who had at least one major congenital malformation was between 2,150 (low range) and 4,100 (high range).[59] The Court of Auditors (Cour des Comptes) have estimated that 10,290 children may meet the compensation criteria[60] for the ONIAM fund.[61]

[58] Health Service Exective (Ireland), Rapid assessment of the number of women and children exposed to sodium valproate in Ireland 1975-2015. Published August 2018.
[59] ANSM. Exposition in utero à l'acide valproïque et aux autres traitements de l'épilepsie et des troubles bipolaires et risque de malformations congénitales majeures (MCM) en France (2017).
[60] Note that the categories of people able to apply to the ONIAM fund include: the person affected by valproate exposure in utero, the parents or guardians of a minor who was affected by valproate exposure in utero, the legal representative or public guardian of a vulnerable adult, the heir of someone affected by valproate exposure in utero, or any other person who considers that they have suffered damage. Further information can be found on the ONIAM website here: https://www.oniam.fr/valproate
[61] Casassus, B. France bans sodium valproate use in case of pregnancy. The Lancet 2017: **390**, 217

3 Emerging data on the risk of valproate use during pregnancy

24. At the time of licensing of sodium valproate, there were concerns about the teratogenicity of all antiepileptic drugs. The sodium valproate timeline (Annex C) gives an overview of several key papers and warnings published from the 1960s to date. Professors Clayton-Smith, Turnpenny and Wood, and Dr Bromley, provided the Review with an overview of the significant research which has contributed to the understanding of the risks of valproate use in pregnancy,[62] and the patient groups have shared a number of significant papers with the Review. In this Annex, we give a brief overview of this research.

Data on the teratogenicity of all anticonvulsant drugs

25. Letters and papers published around this period primarily focussed on phenobarbital and phenytoin (or other hydantoins), but also included primidone, ethosuximide, troxidone, diazepam and others. A number of these studies considered anticonvulsant drugs as a group, and reported effects including prolonged bleeding in the newborn, neural tube defects, cleft lip or palate, congenital heart disease, limb deformities, hypospadias.[63] Many of these papers concluded that anticonvulsant therapy was necessary during pregnant, and that these drugs should not be withheld on the limited evidence available.

[62] This can be found in full in their written evidence to the Review.

[63] *For example see:* Blomstedt, Y et al. Partnerships for child health: capitalising on links between the sustainable development goals. BMJ 2018: 360, k125; Fedrick, J. Epilepsy and Pregnancy: A Report from the Oxford Record Linkage Study. BMJ 1973: 2, 442; Hill, RM et al. Infants exposed in utero to antiepileptic drugs: A prospective study. American Journal of Diseases of Children 1974: 127, 645-653; Lawrence, A. Anti-epileptic Drugs and the Foetus. British Medical Journal 2018: 2, 1267; Lowe, CR. Congenital malformations among infants born to epileptic women. The Lancet 1973: 301, 9-10; Millar, JHD and Nevin, NC. Congenital malforamtions and anticonvulsant drugs. The Lancet 1973: 301, 328; Speidel, BD, and Meadow, SR. Maternal epilepsy and abnormalities of the fetus and newborn. The Lancet 1972: 2, 839-843.

26. Additionally, specific syndromes with characteristic features were described in case series including 'Fetal phenytoin syndrome' in 1973,[64] 'Fetal hydantoin syndrome' in 1975,[65] and a 'Fetal trimethadione syndrome' in 1975.[66]

Data about the risk of congenital malformations associated with sodium valproate

27. Throughout the 1980s a number of case reports were published, which presented children with a history of valproate exposure and a major congenital malformation,[67] including abnormal facial features, congenital cardiac abnormalities, and limb abnormalities. In 1982, a group report from a French Birth Defect Register suggested an increased risk of spina bifida associated with VPA exposure.[68] These findings were replicated by other birth defect registers,[69] and cases were reported to the Committee on Safety of Medicines (CSM) in the UK.[70]

28. In 1984, DiLiberti and colleagues[71] described a 'Fetal Valproate Syndrome' in seven patients. The features included a specific facial appearance (distinct to that associated with other AEDs), two male patients also had hypospadias, strabismus, and development delay. This was followed by small study in 1986 which found seven

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[64] Loughnan, P et al. Phenytoin teratogenicity in man. The Lancet 1973: 301, 70-72
[65] Hanson, JW et al. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. The Journal of Pediatrics 1976: 89, 662-668
[66] Lietman, PS et al. The fetal trimethadione syndrome. The Journal of Pediatrics 1975: 87, 280-284
[67] *For example see*: Bailey, CJ, et al. Valproic acid and fetal abnormality. BMJ (Clin Res Ed) 1983: 286(6360):190; Bantz, EW. Valproic acid and congenital malformations. A case report. Clinical Pediatrics 1984: 23(6):352-3; Bjerkedal, T et al. Valproic acid and spina bifida. The Lancet 1982: 2(8307):1096; Brown, NA, et al. Teratogenic potential of valproic acid. The Lancet 1980: 1(8169):660-1; Clay, SA, et al. Possible teratogenic effect of valproic acid. The Journal of pediatrics 1981: 99(5):828; Garden, AS, et al. Valproic acid therapy and neural tube defects: Canadian Medical Association Journal 1985: 132(8):933-936; Gomez, MR. Possible teratogenicity of valproic acid. The Journal of pediatrics 1981: 98(3):508-9; Koch, S, et al. Possible teratogenic effect of valproate during pregnancy. The Journal of pediatrics 1983: 103(6):1007-8; Robert, E and Guibaud, P. Maternal valproic acid and congenital neural tube defects. The Lancet 1982: 2(8304):93; Winter, RM, et al. Fetal valproate syndrome: Is there a recognisable phenotype? Journal of Medical Genetics 1987: 24(11):692
[68] Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. Lancet (London, England). 1982;2(8304):937.
[69] *For example see*: Bertollini, R et al. Maternal epilepsy and birth defects: a case-control study in the Italian Multicentric Registry of Birth Defects (IPIMC). European journal of epidemiology 1985: 1(1):67-72; Kallen, B, et al. Anticonvulsant drugs and malformations is there a drug specificity? European journal of epidemiology 1989: 5(1):31-6.
[70] Oakeshott P HG. Valproate and spina bifia. The Lancet. 1989:611.
[71] J. H. DiLiberti, P. A. Farndon, N. R. Dennis, C. J. Curry, The fetal valproate syndrome. *Am J Med Genet* **19**, 473-481 (1984)

infants had a pattern of craniofacial and digital anomalies which was different to that found with exposure to other AEDs.[72] Winter and colleagues reported four further cases in 1987,[73] and Ardinger and colleagues[74] reported on 19 patients exposed to valproate, both agreeing with DiLiberti, and noting that developmental delay had been identified in some patients, and needed to be explored further.

29. Prospective studies began to be established in 1983. This provided better information on the risks associated with valproate exposure, rather than starting with children who had presented to clinicians with problems. Early investigations often reported all AED exposure as a single group, which made it difficult to ascertain the risk of individual AEDs.

30. A collaboration by a number of European groups in 1997 who highlighted an association between valproate exposure and an increased risk of major congenital malformations, noted that there was a dose response, with doses about 1000mg per day being associated with an increased risk of congenital malformations.[75]

31. Other malformations reported include: hernias,[76] tallipes equinovarus ('club foot'),[77] and Kidney abnormalities.[78] Clayton-Smith and colleagues draw attention to the fact that rates of major congenital malformations represent only the most severe structural abnormalities. Children with a history of valproate exposure are at an increased risk of minor malformations (physical health problems which do not require surgical intervention or significant treatment), but which nevertheless may impact on

[72] Jäger-Roman, E., et al. (1986). "Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid." The Journal of Pediatrics **108**(6): 997-1004.
[73] Winter, R. M., et al. (1987). "Fetal valproate syndrome: is there a recognisable phenotype?" Journal of Medical Genetics 24(11): 692-695.
[74] Ardinger, H. H., et al. (1988). "Verification of the fetal valproate syndrome phenotype." American Journal of Medical Genetics **29**(1): 171-185.
[75] Samrén EB et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia. 1997 Sep; 38(9):981-90.
[76] Ardinger, HH et al., Verification of the fetal valproate syndrome phenotype. American Journal of Medical Genetics 1988: 29, 171-185
[77] i*bid.*
[78] Ozkan, H et al. Severe fetal valproate syndrome: combination of complex cardiac defect, multicystic dysplastic kidney, and trigonocephaly. J Matern Fetal Neonatal Med 2011: 24, 521-524

their daily functioning. This includes: facial dysmorphism, hypotonia, overlapping digits, and bladder function difficulties.[79]

Neurodevelopmental effects

32. Early reports of development delay arose in case reports in 1980s.[80] Clayton-Smith and colleagues[81] argue that all of the early studies which looked at development and IQ in the offspring of mothers taking AEDs during pregnancy could be criticised because of inadequate study design, for example analysing all AED exposed children together, or due to the small size of the VPA exposed group. A study by Moore and colleagues[82] in 2000 reported that in children of school age or elder exposed to AEDs, 74% required educational support. A study by Adab and colleagues, reported that 45% of children exposed to valproate monotherapy needed additional help in school, 3.4 times more likely than unexposed children of mothers with epilepsy.[83] Dean and colleagues in 2002[84] found a high level of 'developmental delay' in children with a history of valproate exposure, with delays commonly reported in speech development.

33. Prospective studies, such as the NEAD study, demonstrated that the IQ and reasoning scores of children exposed to valproate was lower than that of children exposed to

[79] Professor Jill Clayton-Smith, Dr Rebecca Bromley, Professor Peter Turnpenny, Professor Amanda G Wood written evidence to the Review
[80] *For example see*: Ardinger et al. Verification of the fetal valproate syndrome phenotype. American Journal of Medical Genetics 1988: 29(1): 171-185; DiLiberti et al. The fetal valproate syndrome. American Journal of Medical Genetics 1984: 19, 473-481; Winter et al. Fetal valproate syndrome: is there a recognisable phenotype? Journal of Medical Genetics 1987: 24(11): 692-695
[81] Clayton-Smith and colleagues written evidence to the review (as above)
[82] Moore, SJ et al. A clinical study of 57 children with fetal anticonvulsant syndromes. Journal of medical genetics. 2000;37(7):489-97.
[83] Adab, N et al. Additional educational needs in children born to mothers with epilepsy. Journal of neurology, neurosurgery, and psychiatry. 2001;70(1):15-21.
[84] Dean, JCS et al. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. Journal of medical genetics. 2002;39(4):251-9.

other AEDs.[85] A dose relationship has been found in cohorts from the UK,[86] America,[87] Australia[88] and Georgia.[89]

34. The neurodevelopmental effects reported include impacts on verbal related skills, language development, executive functional skills[90] and memory skills.[91] 11% of the patients exposed to valproate in the series reported by Moore et al had ASD. Rasalam and colleagues[92] also found the prevalence of ASD in children exposed to AEDs was 8 to 18 times higher than in the general population, the highest in the valproate group (8.9% compared to the population level of 0.25%). Further evidence from prospective studies in the UK,[93] and a population study in Demark[94] provided further evidence.

35. In parallel to observations in congenital malformations, Clayton-Smith and colleagues draw attention to individuals having sub-diagnostic levels of social and communication difficulties which impact their daily functioning, and in individuals who do not have major congenital malformations.[95]

Data from registries

36. A number of registers were established in the 1990s, which collected prospective data on AEDs and pregnancy. This includes the UK Epilepsy and Pregnancy Register, the North American Antiepileptic Drug Register, the Australian Pregnancy Register of

[85] Meador, KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet neurology 2013: 12(3):244-52.
[86] Baker, GA, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: A controlled cohort study. Neurology. 2015;84(4):382-90.
[87] Meador, KJ et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. The New England journal of medicine 2009: 360(16):1597-605; Meador, KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet neurology 2013: 12(3):244-52.
[88] Nadebaum, C et al. Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. Journal of the International Neuropsychological Society 2011: 17(1):133-42.
[89] Kasradze, S et al. Cognitive functions in children exposed to antiepileptic drugs in utero - Study in Georgia. Epilepsy & behavior. 2017;66:105-12
[90] Baker et al, and NEAD studies as above
[91] Barton, S et al. Memory dysfunction in school-aged children exposed prenatally to antiepileptic drugs. Neuropsychology 2018;32(7):784-96.
[92] Rasalam, A et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Developmental Medicine & Child Neurology. 2005;47(8):551-5.
[93] Ref C-S(31, 92)
[94] Christensen, J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013: 309(16):1696-703.
[95] Clayton-Smith et al written evidence to the Review

Antiepileptic Drugs, and EURAP – an International Register of Antiepileptic Drugs and Pregnancy. Outcomes of these registries has been summarised in Cochrane Reviews (see the table below).

Table F.2 *Cochrane Reviews relating to epilepsy and pregnancy*

Year	Reference	Key results/conclusions
2004 Cochrane Systematic Review - Intervention	Adab N, Tudur Smith C, Vinten J, Williamson PR, Winterbottom JB, McKay AJ, Bromley R. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD004848. DOI: 10.1002/14651858.CD004848.pub2. (*Review withdrawn as superseded by new reviews*)	Part 1b – Neurodevelopmental effects. The authors stated that the majority of studies were of limited quality. There was little evidence about which specific drugs carry more risk than others to the development of children exposed in utero. They found that results between studies are conflicting. They also warned that while most studies failed to find a significant detrimental effect of exposure to CBZ, PHT, or PB, these results should be interpreted cautiously. In addition, they found few studies of exposure to sodium valproate. Polytherapy exposure in utero was more commonly associated with poorer outcomes, as was exposure to any AEDs when analysis did not take into account type of AED. The authors suggested that the latter may reflect the large proportion of children included in these studies who were exposed to polytherapy. Conclusions: *Based on the best current available evidence it would seem advisable for women to continue medication during pregnancy using monotherapy at the lowest dose required to achieve seizure control. Polytherapy would seem best avoided where possible. More population based studies adequately powered to examine the effects of in utero exposure to specific monotherapies which are used in everyday practice are required.*
2008 Cochrane Systematic Review -	Winterbottom JB, Smyth RMD, Jacoby A, Baker GA. Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome. Cochrane	The authors found no studies which met the criteria for inclusion in the review. Conclusions: *There is no evidence to inform the content, methods of delivery or effectiveness of preconception counselling to improve pregnancy outcomes for WWE and their offspring. The value of counselling delivered to WWE prior to conception, with the intention of reducing the*

Intervention	Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006645. DOI: 10.1002/14651858.CD006645.pub2. (Review reconsidered in 2014, and withdrawn due to submission of new protocol: doi: 10.1002/14651858.CD011007)	*risks of adverse outcome in mother and child, requires evaluation in well-designed studies, appropriately powered to detect changes in both maternal and infant outcome.*
2014 Cochrane Systematic Review - Intervention	Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD010236. DOI: 10.1002/14651858.CD010236.pub2.	*DQ – Developmental quotient* *IQ – Intelligence quotient* CBZ – DQ lower than children born to women without epilepsy and untreated epilepsy – however further analysis suggests this is due to variability in the studies CBZ – IQ not lower than children born to women without epilepsy or untreated epilepsy VPA – DQ lower than in children of women with untreated epilepsy and without epilepsy. Also had lower IQ than children born to women with untreated epilepsy. In younger children, no significant difference in DQ in CBZ and VPA exposure. IQ of VPA exposed significantly lower than CBZ CBZ – IQ not significantly different to LTG, DQ not significantly different to PHT VPA – IQ significantly lower than LTG, IQ and DQ lower than PHT VPA – dose effect reported in six studies, higher doses (800-1000 mg and above) associated with poorer cognitive outcome in the child No dose effect found for CBZ, PHT, LTG Conclusions: *The most important finding is the reduction in IQ in the VPA exposed group, which*

		are sufficient to affect education and occupational outcomes in later life. However, for some women VPA is the most effective drug at controlling seizures. Informed treatment decisions require detailed counselling about these risks at treatment initiation and at pre-conceptual counselling. We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.
2016 Cochrane Systematic Review - Intervention	Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224. DOI: 10.1002/14651858.CD010224.pub2.	CBZ – higher risk than children born to women without epilepsy or untreated epilepsy PB – higher risk than children born to women without epilepsy PHT – higher risk than children born to women without epilepsy or untreated epilepsy TPM – Increased risk compared to children born to women without epilepsy VPA – higher risk than children born to women without epilepsy or untreated epilepsy LTG - No increased risk GBP, LEV, OXC, PRM, ZNS – not associated with increased risk, but fewer data VPA highest risk of malformation. Increased risk compared to CBZ, GBP, LEV, LTG, TPM, OC, PB, ZNS CBZ increased risk compared to LEV, LTG PB increased risk compared to GBP, LEV, LTG PHT – higher risk than LTG. Comparison to LEV not significant. TMP – higher risk than LEV and LTG <u>Specific malformations</u> PB – associated with cardiac malformations VPA – associated with neural tube, cardiac, oro-facial/cranio-facial, skeletal and limb Dose exposure mediates risk in VPA, dose-response in other AEDs less clear

		Conclusions: *Exposure in the womb to certain AEDs carried an increased risk of malformation in the foetus and may be associated with specific patterns of malformation. Based on current evidence, LEV and LTG exposure carried the lowest risk of overall malformation; however, data pertaining to specific malformations are lacking. Physicians should discuss both the risks and treatment efficacy with the patient prior to commencing treatment.*
KEY CBZ – carbamazepine, GBP – gabapentin, LEV – levetiracetam, LTG – lamotrigine, OXC – oxcarbazepine, PB – phenobarbital, PHY – phenytoin, PRM – primidone, TPM – Topiramate, VPA – valproate, ZNS – zonisamide		

4 Key information changes related to use of Epilim in pregnancy in the Datasheet/Summary of Product Characteristics (SmPC) and the Patient Information Leaflets in the UK

The most recent materials related to Epilim are available on the electronic medicines compendium: https://www.medicines.org.uk/emc/product/519/

Table F.3 *Key information changes in the Datasheet, SmPC and Patient Information Leaflet related to use of Epilim in pregnancy*

Year	Datasheet/Summary of Product Characteristics (SmPC)	Patient Information Leaflet
1974 (Datasheet)	From 1974 onwards, Data sheet included a warning for women of child-bearing age (WoCBA) on valproate: Uses: should 'only be used in severe cases or in those resistant to other treatment'. Contraindications, warnings, etc. Precautions – women of childbearing 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.'*	

1977-83	Wording: 'Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals...'	
1984/5	The wording is updated to include: "…and their pregnancies should be carefully monitored". It now includes information about breast feeding: "...there appears to be no contraindication to breastfeeding by patients on Epilim"	
1986/7	Information on breastfeeding is updated to include: "The decision to allow the patients to breastfeed should be taken with regard to all the known facts."	
1989		**First PIL** *'Things to remember about Epilim'* "If you are likely to become pregnant, tell your doctor" *Details page:* BEFORE TAKING YOUR MEDICINE: Are you pregnant or likely to become pregnant? AFTER TAKING YOUR MEDICINE: Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.
1990-92	'Increased incidence of congenital abnormalities in off-spring born to mothers with epilepsy both untreated and treated has been demonstrated. There have been reports of foetal abnormalities 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-fetoprotein 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.'	
1993/4	Include descriptions of congenital abnormalities (facial dysmorphia, neural tube defects, multiple malformations)	**[Legislation set out form and content of PIL, to apply to all new and renewal of licences after 31 December 1993]**
1994/5	"abnormal pregnancy outcome tends to be associated with higher total daily dosage…", increase screening, and include folate supplementation.	1994 August 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% [*note increases to 1-2% in 1996 version*] 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 <u>as soon as you know</u> you are pregnant. Breast feeding: Very little Epilim gets in the breast milk but you should discuss with your doctor whether you should breast feed your baby.
1997		1997 September

		Addition: There may also be blood clotting problems in the newborn if the mother has taken Epilim during pregnancy.
1998/9	Divide doses to reduce peak plasma concentration	
2001 (SmPC)	Specifically states potential teratogenic risk. Information rearranged in line with recommendations.	[New format PIL, same information]
2003	Includes information on neural tube defects, including a higher risk at a dose above 1000mg. Overall rate of malformations demonstrated 2-3 times higher than rate in general population (3%). Includes association with developmental delay. Advises prolonged release formation.	Information re-ordered. *[Bit difficult to read]* Pregnancy 'Ask your doctor or pharmacist for advice before taking any medicine. It is essential that you discuss your epilepsy treatment with your doctor before you become pregnant. If at any time you suspect that you might already be pregnant you must tell your doctor immediately.' Same risk, but specifies folic acid of 5mg daily as soon as you stop contraception… 'There is also an increased risk of other birth defects. These can usually be detected in the first part of the pregnancy… Infants born to mothers who took Epilim during pregnancy may develop less quickly than normal. This may 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 may 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.(same advice as before)
2005	Potential contributions to developmental delay risk (genetic, social, environmental, maternal epilepsy, antiepileptic	2005 June "Before you start treatment your doctor should discuss with you the problems that may arise if Epilim is used in pregnancy.

	treatment). More detail on developmental delay including verbal IQ.	Unplanned pregnancy is not desirable in women receiving Epilim. You should use an effective method of contraception and consult your doctor before planning pregnancy… It is known that women receiving Epilim during pregnancy have a higher risk that other women of giving birth to a child with an abnormality. The likelihood of abnormalities is increased if you also taking antiepileptic medicines at the same time. These effects include: (gives list of known congenital abnormalities), information on neural tube defects Update: Some babies born to mother who took Epilim during pregnancy may develop less quickly that normal **and may require additional educational support.** Addition: <u>Information for Women who are planning to get pregnant –</u> includes guidance as before to consult doctor for planning/if you're pregnant "in order to receive appropriate counselling ant to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy"
2010	2010 – 'Special warning' for women of childbearing potential and of discussing the risk-benefit before first prescribing and when planning pregnancy. Emphasises need for appropriate counselling. Less detail on the risk relative to the general population of malformations. Inclusion of risks associated with seizures. Further confounding variables regarding developmental	May/Oct 2010 Update: 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.

	delay/verbal IQ (low maternal IQ, poor maternal seizure control). Includes "Autism Spectrum Disorders have also been reported in children exposed to valproate in utero". Gives advice further to those warnings.	Update to 'Women who are planning to get Pregnant' section to set out doctors' actions: appropriate counselling, suggest changes to treatment or dose, check progress while pregnant. Also "It is very important that you discuss your treatment with your doctor well before you become pregnant"
2011	Section reworded. Valproate should not be discontinued without reassessment of the benefit/risk. "Women of child-bearing potential must use effective contraception during treatment" Further detail on risks associated with valproate. More detailed information on prescribing information.	2011 Jun Stronger opening line: **"Women who could become pregnant. You should not take this medicine or you are pregnant or a woman of child-bearing age unless explicity advised by your doctor**" and supporting statement "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.
2012	Include information about meta-analysis. Incidence of congenital malformations in children born to epileptic women exposed to VPA monotherapy during pregnancy is 10.73%.	2012 Nov Very slight change to wording. Also includes updates to other effects during pregnancy (hypothyroidism)
2015	As result of PRAC information updated with significant special warnings and precautions • Specialist should supervise • Valproate use only if other treatments not effective/tolerated • Specific instructions to the prescriber on information to be given to the patient including guidance on risks	Updated with significantly more information. **Important advice for women:** • "Valproate can be harmful to unborn children when taken by a woman during pregnancy" • Information on: dose and risk, birth defects, "Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 1000

	• Clear information on female children and female adolescents. • Clearly sets out risks relative to general population. • Information on mental and physical development, including reduction of IQ average 7-10 points. And increased risk of autism spectrum disorder • Increased detail on breastfeeding. • Information on effects on fertility in both men and women.	will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy" • Estimated "up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development." Characterises this. "Autistic spectrum disorders are more often diagnosed in children exposed to valproate"... ADHD. • Gives guidance re: valproate as last resort, doctor's responsibilities to explain risk, and agree plan for pregnancy planning.... • Gives guidance that folic acid reduces general risk of spina bifida and miscarriages, but not the birth defects associated with valproate **First prescription** • Sets out responsibility/actions of doctor • Using effective method of contraception • Tell doctor if you think you are pregnant **Continuing treatment and not trying for a baby** • Re-iterates to make sure using effective method and to tell doctor if think you are pregnant **Continuing treatment and considering trying for a baby** • Do not stop taking valproate/contraceptive until discussed with prescriber

		• Sets out possible steps to manage risk: change dose or switch medicine, close monitoring, folic acid **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" • Inform doctor immediately, do not stop treatment until instructed to by doctor "**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"**
2018	Stronger information regarding female children and women of child-bearing age, and about the PPP.	<u>2018 April</u> Opening section: Important advice for women – overview of risk • "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...." Previously included under 'Important Advice...' now in 'The risks of valproate when taken during pregnancy'

		• Include advice to contact doctor when child experiences their first period Previous sections reordered and clear headings – choose relevant description: • 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 No new advice on risk, but further advice on management (e.g. pregnancy excluded before start of treatment, regular appointments, patient card. <u>2018 June(Aug)</u> Update on interaction with oestrogen-containing oral contraceptives. Additional wording on counselling/monitoring but no change to risk descriptions.
November/ December 2018[96]	2018 Dec Under **'4.2 Posology and method of administration'**	<u>2019 Jan (last revised Nov 2018)</u> **WARNING**:

[96] Relevant sections from the current versions of the SmPC and Patient Leaflet, available on **<u>https://www.medicines.org.uk/emc/product/519/smpc</u>** for Epilim 200mg Gastro-resistant tablets.

	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). **4.4 Special warnings and precautions for use** ***Female children, women of childbearing potential and pregnant women:*** **Pregnancy Prevention Programme**	**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.** '**What you need to know before you take Epilim – Do not take Epilim and tell your doctor if**': • 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.

	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). <u>Conditions of Pregnancy Prevention Programme:</u> 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.*	Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility – Important advice for women'). **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,

	• 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	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).

	compelling reasons to indicate that there is no risk of pregnancy. <u>Female children</u> 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.	• 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).

	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.	**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).

	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. <u>Annual treatment reviews by a specialist</u> 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. <u>Pregnancy planning</u> 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.	**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.

	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. <u>In case of pregnancy</u> 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). <u>Pharmacists must ensure that:</u> • 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.	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

	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. **4.6 Fertility, pregnancy and lactation**	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.

	• 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. <u>Teratogenicity and developmental effects</u> *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.	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.**

	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	**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.

	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. <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. <u>Breast-feeding</u> 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. <u>Fertility</u> 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.	

5 Information on dosage

37. One concern that has been raised by patient groups and individuals who have contacted the Review is that some women were prescribed excessive doses of Epilim. Guidance to prescribers in the datasheet and SmPC about the maximum dose in adults has not been higher than 2,600mg/day, and is currently at 2,500mg/day. Advice on dosage and polytherapy in adults since 1977 has recommended that prescribers should aim for optimum control at the lowest possible combined-dosage level (see the table below). Specific information on dosage in pregnancy was not included until 1994. Updates to this are also included in the table below.

Table F.4 *Information on Epilim dosage in pregnancy available via the datasheet and SmPC*

Date	General dosage advice (for adults)	Pregnancy dosage advice
1975	Start at 200mg twice per day. Control usually – 800 – 1,400mg/day (over two/three doses), increase up to 2.4g/day in severe cases. May be possible to reduce or withdraw other medication if Epilim is effective. If sedation observed, reduce barbiturates.	None
1977	Start at 600mg/day, divided doses. Control usually 1000-1,600 mg/day. Maximum 2,500 mg/day, or add another AED. Adjust Epilim and other agents to give optimum control at lowest possible combined-dosage level.	None
1978	Some additional advice about the 200 and 500 mg tablets. Maximum increased during that period to 2,600 mg/day.	None
1982-3	Information provided about dose/plasma level ratio, and dosage in polytherapy.	None
1984-5	Change in layout – sets out monotherapy and polytherapy separately. Monotherapy: Dosage start at 600mg/day. Control usually 1000-2000mg/day (20-30mg/kg body weight). Increased to 2,500mg/day. Combined therapy: May be necessary to	None

	raise by 5-10 mg/kg/day when used in combination with ACD which induce liver enzyme activity. Optimum dose determined by seizure control.	
1994-5		Anticonvulsant monotherapy preferred. Dosage should be reviewed before conception and lowest effective dose use as abnormal pregnancy outcome tends to be associated with higher total daily dosage.
1998-1999		'…lowest effective dose used, in divided doses as abnormal pregnancy outcomes tends to be associated with higher total daily dosage'
2003		'…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 formation is preferable in order to avoid high peak plasma levels.'
2015	Information in the Posology section drawing attention to 'Female children, female adolescents, women of childbearing potential and pregnant women.' Epilim should be prescribed as monotherapy, at the lowest effect dose, as a prolonged release formation and in divided daily loses, to avoid high peak plasma concentrations.	Congenital malformations: 'The risk is dose dependent but a threshold dose below which no risk exists cannot be established.' Developmental disorders: 'The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data.' If want to plan a pregnancy: 'Preferably Epilim should be prescribed as monotherapy..' '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.'

2018	Updated to include information in Posology section – 'Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme'. Should be prescribed as monotherapy and at the lowest effective dose, if possible as prolonged release formulation. Daily dose should be divided into at least two single doses.	PPP in detail. Advice related to dosage as 2015.

6 Warnings from the Regulator in the UK

38. The key sources of information to doctors are the communications to doctors from UK regulatory bodies, the British National Formulary (BNF), and the NICE guidelines.

Direct communication to doctors

39. The general advice communicated in the 1973 CSM Annual Letter to Doctors was: "Meanwhile it is now clear from other studies that the use of anti-convulsants during pregnancy… is liable to produce other abnormalities as well as harelip and cleft-palate. The risk appears to be low and not sufficient to justify stopping the use of anti-convulsants when they are necessary for the control of epilepsy."[97]

Patient Safety Alerts

40. A Patient Safety Alert was issued by the MHRA and NHS Improvement in April 2017, [98] further to the toolkit, to "ask all organisations to undertake systematic identification of girls and women who are taking valproate, and ensure the MHRA resources are used to support them to make informed choices."

Current Problems and the Drug Safety Update

41. The Current Problems series by the Committee on Safety of Medicines (CSM) was intended to draw attention to matters of concern or interest which had been considered by the CSM. It was hoped that this would facilitate information flow to and from the Committee. It was replaced by the 'Drug Safety Update', a monthly electronic bulletin with information and clinical advice from the MHRA and CHM about the safe use of medicines. An overview of the relevant articles is included in the table below.

[97] 1973 CSM Annual Letter to Doctors, quoted in MC 76/112A 'A Note on Epilim – Sodium Valproate' 1976 (see MHRA written evidence to the Review)
[98] MHRA and NHS Improvement. 6th April 2017. Patient Safety Alert: Resources to support the safety of girls and women who are being treated with valproate. Ref: NHS/PSA/RE/2017/002. Link here.

***Table F.5* Overview of articles in 'Current Problems' and 'Drug Safety Update'**

Date	Title	Summary
Current Problems		
February 1981 (Number 5)	Medicines in Pregnancy	"*Recent publicity about reports of suspected damage to the fetus following the administration of drugs during pregnancy has led to widespread concern. The Committee on Safety of Medicines and the Committee on the Review of Medicines are constantly aware of the importance of considering the possible teratogenic effects of drugs. Because of the "background" incidence of congenital abnormality, of unknown aetiology, it is difficult to establish a causal relationship between a particular drug and fetal damage. At the same time it is impossible to prove beyond a shadow of a doubt that any drug is absolutely safe in pregnancy. The CSM supports the view that drugs should not be given during pregnancy unless they are essential.*"
July 1981 (Number 6)	Sodium valproate (Epilim)	Contains overview of reported side effects including: prolongation of bleeding time and thrombocytopenia; liver damage; hyperammonaemia; acute pancreatitis. There are no warnings related to valproate exposure in utero.
January 1983 (Number 9)	Sodium Valproate (Epilim) and Congenital Abnormalities	The article notes the increased incidence of congenital malformations in children exposed to AEDs in utero, and recent data regarding an apparent association between sodium valproate exposure and neural tube defects. It discusses the difficulty in interpreting results, including determining the extent to which the medication or the disease has an effect. It advises that treatment should not be withdrawn due to the risk of foetal hypoxia due to maternal seizures. It concludes that there is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other.
December 1986[99]	*CSM/CRM Update in the BMJ: Pregnancy warnings in data sheets*	*Update published by the CSM/CRM in the BMJ. Recommended that warnings should be included in data sheets to enable a doctor to make a balanced assessment between risks to fetus and benefits to mother. This should include information on animal data, human population studies and*

[99] CSM/CRM Update: Pregnancy warnings in data sheets. BMJ (Clin Res Ed) 1986: 293:1495 doi: 10.1136/bmj.293.6560.1495

		anecdotal reports, and guidance on interpretation. Specimen warnings were also provided. This listed the following antiepileptic drugs as being suspected human teratogens: • Ethosuximide - may be teratogenic • Phenytoin - congenital malformations • Sodium valproate - increased risk of neural tube defects reported
February 1993 (Vol 19)	In Focus: Lamotrigine (Lamictal)	[Marked with black triangle to indicate continued monitoring] Summary of lamotrigine (introduced in November 1991). Lists dermatological, psychiatric, neurological and gastrointestinal reactions as adverse reactions reported to the CSM/MCA. There are no warnings related to AED exposure in utero.
June 1993 (Vol 19)	Neural tube defects associated with sodium valproate and carbamazepine – need for counselling and screening.	Within the 'Reminder' section: "***Neural tube defects associated with sodium valproate and carbamazepine – need for counselling and screening.*** • The use of sodium valproate or carbamazepine in early pregnancy is associated with an increased risk of neural tube defects. • Women taking these drugs who may become pregnant should be informed of the possible consequences. • Those who wish to become pregnant should be referred to an appropriate specialist for advice. • Women who do become pregnant should be counselled and offered ante-natal screening (alpha-fetoprotein measurement and a second trimester ultrasound scan)."
September 1997 (Vol 23)	Reminder: Avoid benzodiazepines in pregnancy and lactation.	Reminder that benzodiazepines cross the placenta and may lead to physical dependence in infants exposed in utero, as well as hypotonia, hypothermia and moderate respiratory depression of administered in high doses during late pregnancy or labour. Benzodiazepines are also excreted in breast milk and should not be given to lactating mothers.

September 2003 (Vol 29)	Sodium valproate and prescribing in pregnancy	The key messages included: • The risk of congenital malformations following in-utero exposure to AEDs is approximately 2 to 3 times higher than in the general population • In utero exposure to sodium valproate has been associated with an increased incidence of congenital malformations including facial dysmorphia, and multiple malformations, particularly of the limbs • Two retrospective epidemiological studies have also suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Other factors, such as the mother's epilepsy, may also contribute to this risk. • Sodium valproate remains the anti-epileptic of choice in patients with certain types of epilepsy 42. Following a review of the available data including data from the UK Pregnancy and Epilepsy Register, the CSM advised: • Specialist neurological advice prior to starting sodium valproate • Pre-conception counselling for women on sodium valproate • If taken during pregnancy, sodium valproate should be prescribed as monotherapy, at the lowest effective dose, in divided doses, and as a prolonged release preparation. • Folic acid supplementation may reduce risk of neural tube defects
Drug Safety Update		
November 2013 (Vol 7 Issue 4)	Sodium valproate: Risk of neurodevelopmental delay in children following maternal use	Summarises increased risk of birth defects in the children of women who take antiepileptics during pregnancy, and of greater risk of neural tube defects and other specific malformations in those exposed to sodium valproate in utero. Reports on recent studies indicating a risk of long term neurodevelopmental effects including autism spectrum disorders. Links to the review being undertaken by the EMA. Gives advice on use of sodium valproate in women of childbearing age, including:

		• Valproate should not be used during pregnancy and in women of childbearing potential unless clearly necessary; alternatives should be considered if used for bipolar disorder • Counselling should be made available • If used during pregnancy, the lowest effective dose should be used in divided doses • Folate supplementation should be started before pregnancy • Specialist prenatal monitoring should take place
January 2015 (Vol 8 Issue 6)	Medicines related to valproate: risk of abnormal pregnancy outcomes	This update was issued following completion of the European review. The update contained detailed information on risk and set out actions of healthcare professionals. The key points are included here: • Children exposed to valproate in utero have a high risk of serious developmental disorders (up to 30-40%) and/or congenital malformations (10%) • Valproate should not be prescribed in girls and women of childbearing potential unless other treatments are ineffective or not tolerated • Valproate treatment should be started by a doctor experienced in managing epilepsy or bipolar disorder • The balance of benefit and risk should be considered when first prescribed, and reviewed at routine treatment reviews, at puberty, when planning a pregnancy or when a woman becomes pregnant • HCPs must ensure that female patients are informed of and understand: risks associated with valproate use in pregnancy, need for effective contraception; need for regular review of treatment; need to rapidly consult a doctor if planning or becomes pregnant. 43. The update includes further information about educational materials that have been made available for healthcare professionals and patients.

		In addition, it announces that valproate has become a black triangle medicine[100] indicating that any suspected side effects should be reported via the Yellow Card scheme.
February 2016 (Vol 9 Issue 6)	Valproate and risk of abnormal pregnancy outcomes: new communication materials	Refers to risks summarised in January 2015 Update (above). This update provides new communication materials to support discussion of risks (healthcare professional booklet, checklist to go through with patient and file in medical records, patient information guide and patient card) – referred to as the valproate 'toolkit'. It notes that hard copies of these materials are being sent in the post, and that later in 2016 outer packaging for valproate containing medicines will include a warning for women on the risk of pregnancy outcomes. It notes that effectiveness of these risk minimisation measure will be monitored via prescribing data and evaluation of levels of patient awareness. The guidance also includes a statement that the risks and advice of the article also apply to the 'off-label' use of valproate for migraine or chronic pain.
March 2016 (Vol 9 Issue 8)	Letters sent to healthcare professionals in February 2016	Notification of letter sent to healthcare professionals in February 2016, regarding new communication materials about medicines containing valproate and the risk of abnormal pregnancy outcomes.
April 2017 (Vol 10 Issue 9)	Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures	Update to inform that following evidence that women were still not being made aware of the risk of valproate medications during pregnancy, a patient safety alert was issued.[101] A new European review was considering whether further regulatory action was required. The update repeats information on risks, advice for healthcare professionals and links to the supporting educational materials.

[100] Introduced in the UK to highlight medicines subject to intensive safety monitoring, since 2013 the black triangle ▼ has been part of an EU-wide scheme to indicate 'additional monitoring', and that suspected adverse reactions should be reported. Website.

[101] MHRA and NHS Improvement. 6th April 2017. Patient Safety Alert: Resources to support the safety of girls and women who are being treated with valproate. Ref: NHS/PSA/RE/2017/002. Link here.

August 2017 (Vol 11 Issue 1)	Letters sent to healthcare professionals in July 2017	Notification of letters sent to healthcare professionals, to supplement the previous communications and patient safety alert. These set out the actions required by specialists, specialist nurses/midwives, and general practitioners, and for pharmacists, referring to material provided previously.
April 2018 (Vol 11 Issue 9)	Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met	Advises that valproate is now contraindicated in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place. • Gives overview of the risks and new regulatory measures following the EU Review • Sets out the conditions of the Pregnancy Prevention Programme • Informs that materials will be sent by post (Patient Guide, Healthcare Professional Guide, Risk Acknowledgement Form, and for pharmacists, Patient Cards and stickers to attach to the pack) [*links provided in May 2018, Risk Acknowledgement Form updated March 2019*] • Actions for GPs - identify and recall all girls and women of childbearing potential, provide the Patient Guide, check they have been reviewed by a specialist in the past year and are on highly effective contraception • Actions for specialists – annual reviews under the PPP, complete and sign the Risk Acknowledgement Form • Actions for pharmacists – ensure dispensing in whole packs, include warning label, and discuss risks with female patients, ensuring they have seen their GP or specialist, and have the relevant educational material • Informs of contraindication in bipolar disorder • Reminder that adverse reactions associated with valproate, including adverse pregnancy outcomes, should be reported to the Yellow Card Scheme • Sets out what 'highly effective' contraception includes • Informs that visual warning symbol will be added to packets by September 2018 • Notification that search and audit function for GPs will be put in place by GP systems suppliers, and prescribing alerts will be updated • Links to guidance published in March 2018.

May 2018 (Vol 11 Issue 10)	Valproate medicines (Epilim▼, Depakote▼): Pregnancy Prevention Programme materials online	Notification that Patient Guide, Healthcare Professional Guide, Risk Acknowledgement Form, and Patient Cards now online. Gives overview of who should be on a Pregnancy Prevention Programme. Provides reminder about restrictions and responsibilities regarding off-label use. The update also encourages healthcare professionals to share best practice.
August 2018 (Vol 12 Issue 1)	Letters and drug alerts sent to healthcare professionals in July 2018	Dear Healthcare Professional letters were sent by Sanofi to doctors and pharmacists, informing them of "new contraindications, strengthened warnings and measure to prevent valproate exposure during pregnancy." This set out the key information and expected actions related to the pregnancy prevention programme.
Sep 2018 (Vol 12 Issue 2)	Valproate Pregnancy Prevention Programme: actions required now from GPs, specialists, and dispensers	Reminder that valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place, and of responsibilities and actions required by healthcare professionals. Information on how to order more packs. Information on new resources available: • Royal Pharmaceutical Society – Quick Reference Guide for dispensing valproate for girls and women (updated 13 August 2018) • Company Chemists' Association (CCA) audit tool for community pharmacy teams to use in reviewing their support for girls and women taking valproate medicines • MHRA Video 'Valproate – pregnancy prevention programme'
Dec 2018 (Vol 12 Issue 5)	Valproate medicines: are you acting in compliance with the pregnancy prevention measures?	Lists the key new information as: • Compliance by healthcare professionals with the new valproate measures for pregnancy prevention appears currently patchy • Women are not always receiving Patient Information Leaflets with their medicines, as is required • Some women using valproate for off-label indications are not being reviewed in line with the new pregnancy prevention measures • Guidance is available for psychiatrists on the withdrawal of, and alternatives to, valproate in women of childbearing potential

		Provides a reminder for all healthcare professionals and pharmacists of their responsibilities and required actions. Includes further detail on off-label prescribing, non-adherence to regulatory measures, and analysis of the prescribing data.
April 2019 (Vol 12 Issue 9)	Valproate medicines and serious harms in pregnancy: new Annual Risk Acknowledgement Form and clinical guidance from professional bodies to support compliance with the Pregnancy Prevention Programme	Informs that further efforts are required by clinicians to achieve compliance with the valproate Pregnancy Prevention Programme. Reminder of key facts about risks of valproate in pregnancy, advice for healthcare professionals, and updates to the Annual Risk Acknowledgement form. Also includes links to information sources: • NICE summary of guidance and safety advice • Pan-college guidance on valproate use in women and girls of childbearing years • Paediatric guidance on the use of valproate in female patients under 18 years of age

7 The BNF overview of information related to use of valproate in pregnancy

Table F.6 *BNF entries related to use of drugs in pregnancy and valproate use*

BNF #	Year	Entry
	1971	Adverse Reactions **"Hazards of Drugs in Pregnancy, Lactation and the Newborn** *Pregnancy* It is widely accepted that it is unwise to prescribe any drug during pregnancy, especially during the first three months, unless there is good reason. It is equally important that a patient who needs a drug for the treatment of illness such as an infection, epilepsy or hypertension should not be denied it because she is pregnant. The following brief notes indicate drugs for which there is either evidence or suspicion that they cause fetal damage. The proprietary products listed under the drugs are given as examples of simple or of compound preparations containing the drugs. … Phenobarbitone, Phenytoin: In man there is only doubtful evidence that the incidence of cleft palate is increased. No damage due to interference with folic acid metabolism has been noted." Anticonvulsants Regarding anticonvulsants, recommends the following with reference to their use in specific epilepsy forms. States that regimen should be continued until patient has been free from fits for two years. • Phenobarbitone ('after 50 years, remains the drug of first choice in grand mal') • Primidone (mysoline)

		• Phenytoin • Ethotoin (peganone) • Ethosuximide • Paramethodione (paradione) • Troxidone (Triodone) • Sulthiame (ospolot) • Carbamazepine (Tegretol) Summarises the immediate and long-term side effects of these drugs. There is no mention of their use or adverse effects during pregnancy.
	1974-76	<u>Adverse reactions</u> Requests that doctors report adverse reactions through the yellow card scheme. **"Prevention of Adverse Reactions** Never use any drug unless there is good indication. If the patient is pregnant do not use a drug unless the need for it is imperative." <u>Anticonvulsants</u> Same advice as previously. No mention of their use of adverse effects during pregnant.
	1976-1978	<u>Adverse reactions</u> No new information <u>Anticonvulsants</u> Advice updated regarding epilepsy forms, dosage, and drug combinations. • Phenobarbitone no longer drug of first choice in grand mal, many prefer phenytoin • Primidone (mysoline) • Phenytoin • Ethosuximide • Paramethadione • Troxidone

		• "Sodium valproate (Epilim) is being tried as second choice for petit mal and is also being used for grand mal." • Sulthiame • Carbamazepine • Benzodiazepines Lists the immediate and long-term side effects. Does not mention use or adverse events during pregnancy.
1	1981	<u>General information</u> *"Prescribing in Pregnancy* For many drugs there is not sufficient evidence to ensure that they are entirely harmless to the foetus, especially in the first trimester of pregnancy. Special care is therefore required in prescribing for pregnant patients. Medicines should be prescribed only when they are essential and in all cases the benefit of administering the medicine should be considered in relation to the risk involved." <u>Adverse reactions to drugs</u> Pregnancy advice as before <u>4.8 Antiepileptics</u> 4.8.1 Control of Epilepsy *"Pregnancy* Although several antiepileptics are teratogenic in *animals*, the increased risk of congenital malformations is in practice slight. Abrupt withdrawal of antiepileptics also carries risk of increased seizure frequency or status epilepticus." *Tonic-clonic (grand mal) and partial (focal) seizures* "Sodium valproate (Epilim) is active in controlling tonic-clonic fits, particularly if there are primary (idiopathic), but its efficacy compared with the longer established drugs has still to be evaluated. It has little effect on partial seizures." *Absence seizures (petit mal)* "Sodium valproate (Epilim) is effective in simple absence seizures and since, unlike ethosuximide, it will also treat tonic-clonic fits, it may be preferred for absences associated with tonic-clonic fits."

		Myoclonic-atonic seizures (myoclonic jerks) "There are a variety of syndromes occurring in childhood in which myoclonic jerks and atomic seizures occur. They have responded poorly to the traditional drugs. Sodium valproate (Epilim) and clonazepam (Rivotril) are the drugs of first choice. Sodium valproate should be tried before clonazepam, which is more sedating." ***Sodium valproate*** *Indications:* tonic-clonic; absence and myoclonic-atonic seizures *Cautions:* monitor liver function before and at 2-month intervals during first 6 months of therapy; monitor platelet function before major surgery; may give false positive urine tests for ketones in diabetes. Drug interactions: see Appendix 1 [not included] *Side-effects*: gastric irritation, nausea (use e/c tablets); transient hair loss, oedema, thrombocytopenia; impaired liver function leading rarely to fatal hepatic failure *Dose*: initially, 200 mg 3 times daily, increasing by 200 mg per day at 3-day intervals to a max. of 2.6g daily in divided doses, according the patient's needs. [includes dosage for children, and price of the Epilim formulations from Reckitt-Labaz]
2	1981	<u>General Information</u> As before <u>Adverse reactions to drugs</u> Pregnancy advice as before <u>4.8 Antiepileptics</u> Information as before
3	1982	<u>General information</u> As before <u>Adverse reactions to drugs</u>

		Pregnancy advice as before <u>4.8 Antiepileptics</u> 4.8.1 Control of Epilepsy Pregnancy advice as before *Tonic-clonic (grand mal) and partial (focal) seizures* "Sodium valproate (Epilim) is active in controlling tonic-clonic fits, particularly if there are primary (idiopathic), but its efficacy compared with the longer established drugs has still to be evaluated. It has little effect on partial seizures. Routine monitoring is unjustified at present because the activity of the drug may not be accurately reflected by its plasma concentration." *Absence seizures (petit mal)* As before *Myoclonic-atonic seizures (myoclonic jerks)* As before ***Sodium valproate*** Note change to Labaz
4	1982	Specific section introduced <u>Prescribing in Pregnancy</u> "Drugs can have harmful effects on the foetus at any time during pregnancy. During the first trimester they may produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy. Few drugs have been shown conclusively to be teratogenic in man but not drug is safe beyond all doubt in early pregnancy. During the second and third trimesters drugs have affect the growth and functional development of the foetus or have toxic effects on foetal tissues; and drugs given shortly before term or during labour may have adverse effects on the neonate after delivery.

		Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the foetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used. The Table below lists drugs known to have harmful effects in pregnancy and indicates the trimester in which these effects occur. Experience with many drugs in pregnancy is limited. The Table is based on human data and animal toxicological studies have been excluded. Therefore it should be noted that the absence of a drug from the list does not imply safety." *Antiepileptics – risks in the 1st and 3rd trimester – Benefits of treatment outweighs risk to the foetus* Phenytoin, phenobarbitone – risks in the 1st and 3rd trimester – Congenital malformations. Neonatal bleeding tendency – prophylactic vitamin K_1 should be given. <u>Prescribing during Breast-feeding</u> Section is introduced. • Phenobarbitone "Avoid when possible; sedation in infant. Sucking reflex and milk flow inhibited. May induce infant's liver microsomal enzymes" • Phenytoin "May induce liver enzymes. One case of methaemoglobinaemia" • Primidone "Avoid during breast-feeding; sedation in infant" <u>Adverse reactions to drugs</u> Pregnancy advice as before <u>4.8 Antiepileptics</u> 4.8.1 Control of Epilepsy *Pregnancy* Advice as before. *Tonic-clonic (grand mal) and partial (focal) seizures*

		Advice as before *Absence seizures (petit mal)* As before *Myoclonic-atonic seizures (myoclonic jerks)* As before ***Sodium valproate*** *Side effects:* Addition of 'rarely pancreatitis'
5	1983	All entries as for Number 4
6	1983	<u>Prescribing in Pregnancy</u> *Antiepileptics – Benefits of treatment outweighs risk to the foetus* Additions: Ethosuximide – risk in 1st trimester – May possibly be teratogenic Sodium valproate – risk in 1st trimester – May possible be teratogenic <u>Prescribing during Breast-feeding</u> Phenytoin removed from list <u>Adverse Reactions to Drugs</u> *Established drugs* – includes 'effects on fertility' and 'reactions in pregnant women' in list of examples of adverse drug reaction which should be reported to the CSM. *Special problems* – Section on "*Congenital abnormalities:* When an infant is born with a congenital abnormality doctors are asked to regard the abnormality as a possible adverse reaction and to report the all drugs (including self-medication) taken by the mother during pregnancy."

		Advice on prevention of adverse reactions as before. <u>4.8 Antiepileptics</u> No change to entries in this section.
7	1984	<u>Prescribing in Pregnancy</u> Addition to Phenytoin, phenobarbitone – Caution in interpreting maternal plasma phenytoin in the effective (free) phenytoin concentration. <u>Prescribing during Breast-feeding</u> Draws attention to Carbamazepine to be considered under benzodiazepines. Benzodiazepines – avoid repeated doses during breast-feeding; lethargy and weight loss may occur in infant. <u>Adverse Reactions to Drugs</u> *Special problems* – Update to section on "*Congenital abnormalities:* When an infant is born with a congenital abnormality or there is a malformed aborted foetus doctors are asked to regard the abnormality as a possible adverse reaction and to report the all drugs (including self-medication) taken by the mother during pregnancy." <u>4.8 Antiepileptics</u> No change to entries in this section.
8	1984	<u>Prescribing in Pregnancy</u> Change in entry: Sodium valproate – Risk in 1st trimester – "Increased risk of neural tube defects reported but not substantiated" <u>Prescribing during Breast-feeding</u> No change to information <u>Adverse Reactions to Drugs</u> Advice as before

		4.8 Antiepileptics Changes to **Sodium valproate** *Side effects:* gastric irritation, nausea; increased appetite and weight gain; transient hair loss (regrowth may be curly), oedema, thrombocytopenia; impaired hepatic function leading rarely to fatal hepatic failure (see Cautions – withdraw treatment immediately if vomiting, anorexia, jaundice, drowsiness, or loss of seizure control occurs); rarely pancreatitis (estimate plasma amylase in acute abdominal pain).
9	1985	Prescribing in Pregnancy No change Prescribing during Breast-feeding Sodium valproate included in list of 'Drugs present in milk in amounts too small to be harmful' Adverse Reactions to Drugs Advice as before 4.8 Antiepileptics No changes to information
10	1985	No changes to earlier sections. 4.8 Antiepileptics Key changes below: *Tonic-clonic (grand mal) and partial (focal) seizures* "Sodium valproate (Epilim) is active in controlling tonic-clonic fits, particularly if there are primary (idiopathic), ~~but its efficacy compared with the longer established drugs has still to be evaluated~~. ~~It has little effect on partial seizures~~. Routine monitoring is unjustified at present because the activity of the drug may not be accurately reflected by its plasma concentration."

		Sodium valproate [revised entry] *Indications:* all forms of epilepsy *Dose:* max dose changes to 2.5g faily
11	1986	<u>Prescribing in Pregnancy</u> No change <u>Prescribing during Breast-feeding</u> Entries for phenobarbitone and primidone updated to "Avoid when possible; drowsiness may occur but risk probably small. One case of methaemoglobinaemia reported with phenobarbitone and phenytoin." <u>Adverse Reactions to Drugs</u> Advice as before <u>4.8 Antiepileptics</u> [revised entry] *"Pregnancy.* During pregnancy, plasma concentrations of antiepileptics should be frequently monitored as they may fall, particularly in the later stages. There is an increased risk of teratogenicity associated with the use of anticonvulsant drugs, but this is in practice slight and, generally speaking, prescribing in pregnancy should follow the same principles as that in non-pregnant patients. Breast-feeding is acceptable with all the antiepileptic drugs, taken in normal doses, with the possible exception of the barbiturates. See under Prescribing in Pregnancy." *Tonic-clonic (grand mal) and partial (focal) seizures* General information updated to include: "Sodium valproate is highly effective in primary generalised epilepsy, but may be less effective in secondary generalised and partial seizures." [revised entry] "Sodium valproate (Epilim) is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. Plasma concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful. The drug has widespread metabolic effects, and may have dose-related side-effects. There has been recent concern over severe hepatic or pancreatic toxicity, although these effects are rare."

		Atypical absence, atonic and tonic seizures Update to section, no new information on sodium valproate. **Sodium valproate** *Side effects:* gastric irritation, nausea; hyperammonaemia; increased appetite and weight gain; transient hair loss (regrowth may be curly), oedema, thrombocytopenia, and inhibition of platelet aggregation; impaired hepatic function leading rarely to fatal hepatic failure (see Cautions – withdraw treatment immediately if vomiting, anorexia, jaundice, drowsiness, or loss of seizure control occurs); rarely pancreatitis (estimate plasma amylase in acute abdominal pain).
12	1986	Prescribing in pregnancy Update to information on table to include: "Information on animal studies has been included for some newer drugs which its omission might be misleading." No other changes. Prescribing during Breast-feeding No change Adverse Reactions to Drugs Advice as before 4.8 Antiepileptics *Pregnancy* - Change in wording '…There is an increased risk of teratogenicity associated with the use of anticonvulsant drugs~~, but this is in practice slight and~~, generally speaking, prescribing in pregnancy should follow the same principles as that in non-pregnant patients...' No significant changes
13	1987	No changes to earlier sections. 4.8 Antiepileptics

		Changes to following: **Sodium valproate** *Cautions:* in patients most at risk (e.g. children and those with history of liver disease) monitor liver function in first 6 months;… *Contraindications:* active liver disease
14	1987	No changes to earlier sections. 4.8 Antiepileptics Changes to following: **Sodium valproate** *Cautions:* now includes 'pregnancy and breast-feeding (see notes above)'
15	1988	Adverse Reactions to Drugs Advice as before Prescribing in pregnancy Update to table. "Antiepileptics. Benefits of treatment outweighs risk to the fetus; for further comment see section 4.8." Drugs also listed individually. Information as before. Prescribing during Breast-feeding Update to table style. Drugs listed inidividually. Changes to information: Phentyoin: amount too small to be harmful Valproate (redirected from sodium valproate): amount too small to be harmful. 4.8 Antiepileptics No changes
16	1988	Adverse Reactions to Drugs Advice as before

		<u>Prescribing in pregnancy</u> Update to information presentation Update to table: 'Valproate – Risk in 1st and 3rd trimester of pregnancy – Increased risk of neural tube defects reported; neonatal bleeding and hepatotoxicity also reported' <u>Prescribing during Breast-feeding</u> No changes <u>4.8 Antiepileptics</u> No changes
17	1989	No significant changes
18	1989	No significant changes
19	1990	**Edition not found**
20	1990	<u>Adverse Reactions to Drugs</u> Advice as before <u>Appendix 4: Prescribing in pregnancy</u> Moved to appendices. Updates to table: *Antiepileptics* – Benefit of treatment outweighs risk to fetus; risk of teratogenicity greater if more that one drug used; **important:** *see also* carbamazepine, ethosuximide, phenobarbitone, phenytoin, valproate, and section 4.8 *Carbamazepine* (1st trimester) – May be small risk of teratogenesis *Ethosuximide* (1) – May possibly be teratogenic *Phenobarbitone* (1,3) – Congenital malformations. Neonatal bleeding tendency – prophylactic vitamin K_1 should be given

		Phenytoin (1,3) - Congenital malformations. Neonatal bleeding tendency – prophylactic vitamin K_1 should be given. Caution in interpreting plasma concentrations – bound may be reduced but free (i.e. effective) unchanged *Valproate* (1,3) – Increased risk of neural tube defects (screening advised); neonatal bleeding and hepatotoxicity also reported <u>Prescribing during Breast-feeding</u> No changes <u>4.8 Antiepileptics</u> *Tonic-clonic (grand mal) and partial (focal) seizures* Note – gradual shift to carbamazepine, phenytoin and sodium valproate being drug of choice. **Sodium valproate** *Cautions:* update 'pregnancy (**important** see notes above and Appendix 4 (neural tube screening)); breast-feeding..'
22	1991	No changes to Adverse Effects or Breast-feeding sections. <u>Appendix 4: Prescribing in pregnancy</u> Updates to table: *Carbamazepine* (1st trimester) – May be small risk of teratogenesis including increased risk of neural tube defects (screening advised) *Phenytoin* (1,3) - Congenital malformations. Folate supplements should be given to mother (reduced absorption). Neonatal bleeding tendency – prophylactic vitamin K_1 should be given. Caution in interpreting plasma concentrations – bound may be reduced but free (i.e. effective) unchanged <u>4.8 Antiepileptics</u> **Sodium valproate** *Cautions:* now includes 'avoid sudden withdrawal' *Contraindications:* now includes porphyria *Side effects:* now includes 'ataxia and tremor', amenorrhoea, rashes, leucopenia, red cell hypoplasia

		Note: Now Epilim and Epilim IV, Sanofi
25	1993	No changes to adverse reactions or breast-feeding sections. <u>Appendix 4: Prescribing in pregnancy</u> Updates to table: *Phenytoin* (1,3) - Congenital malformations (screening advised). Folate supplements should be given to mother (reduced absorption). Neonatal bleeding tendency – prophylactic vitamin K_1 should be given. Caution in interpreting plasma concentrations – bound may be reduced but free (i.e. effective) unchanged <u>4.8 Antiepileptics</u> More detailed information is included in the general section regarding polytherapy, interactions (signposting to oral contraceptive interactions) and withdrawal. Information related to seizure type is summarised. Individual drugs are then considered in more detail. VALPROATE "Sodium valproate is effective in controlling tonic-clonic seizures, particular in primary generalised epilepsy. It is the drug of choice in myoclonic seizures, and may be tried in atypical absence, atonic, and tonic seizures. Controlled trials in partial epilepsy suggests that it has similar efficacy to that of carbamazepine and phenytoin, but more evidence is awaited. Plasma concentrations are not a useful index of efficacy, therefore routing monitoring is unhelpful. The drug has widespread metabolic effects, and may have dose-related side-effects. There has been concern over severe hepatic or pancreatic toxicity, although these effects are rare." No further changes to information.
26	1993	<u>Appendix 4: Pregnancy</u> Updates to table: *Carbamazepine* – May be small risk of teratogenesis including increased risk of neural tube defects (counselling and screening advised – **important:** see also **CSM** advice, p. 180); folate supplements should be given *Valproate* - also updated to include '(counselling and screening advised – **important:** see also **CSM** advice, p. 180)' <u>4.8 Antiepileptics</u>

		Pregnancy and breastfeeding updated to include the following: "**Important:** in view of the increased risk of neural tube defects associated with carbamazepine and valproate the **CSM** has advised that women taking these drugs who *may become pregnant* should be **informed of the possible consequences** and those who *wish to become pregnant* should be referred to an appropriate specialist for advice. Women who become pregnant should be **counselled** and offered **antenatal screening** (alpha-fetoprotein measurement and a second trimester ultrasound scan)." No further changes.
27	1994	No significant changes relating to pregnancy or breastfeeding
28	1994	<u>Appendix 4: Pregnancy</u> Update to entry for carbamazepine. Trimester 1: as before Trimester 3: Because of neonatal bleeding tendency associated with some antiepileptics, manufacturer advises prophylactic vitamin K1 for mother before delivery (as well as for neonate) No other significant changes relating to pregnancy or breastfeeding
29	1995	No significant changes relating to pregnancy or breastfeeding
30	1995	<u>4.8 Antiepileptics</u> Information on CSM advice boxed for emphasis **Sodium valproate** – increased information related to adverse effects but no changes related to pregnancy or breastfeeding.
31	1996	<u>Appendix 4: Pregnancy</u> Vigabatrin added to table: Congenital anomalies reported – manufacturer advises avoid. <u>4.8 Antiepileptics</u> Updates to *Pregnancy and breast-feeding* section. • Information taken back out of box • Phenytoin added to the list of drugs associated with increased risk of neural tube and other defects

		• Inclusion of following: "To counteract the risk of neural tube defects adequate folate supplements are advised for women before and during pregnancy; in the case of antiepileptics such as carbamazepine and phenytoin, doses of folic acid of the order of 5 mg daily are recommended." • Advises prophylactic Vitamin K1 with CBZ, PB and PHT due to risk of neonatal bleeding • Update to possibly exclude breastfeeding in: barbiturates, ethosuximide, and more recently introduced AEDs
32	1996	No significant changes relating to pregnancy or breastfeeding
33	1997	Appendix 4: Pregnancy Draws attention to the National Teratology Information Service No other significant changes relating to pregnancy or breastfeeding
34	1997	4.8 Antiepileptics *Pregnancy and breast-feeding* – includes line that the increased risk of teratogenicity associated with AEDs is 'reduced if treatment is limited to a single drug'.
35	1998	No significant changes relating to pregnancy or breastfeeding
36	1998	Appendix 4: Pregnancy Addition to valproate – neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported No other significant changes relating to pregnancy or breastfeeding
39	2000	No significant changes relating to pregnancy or breastfeeding
40	2000	4.8 Antiepileptics *Pregnancy and breast-feeding* – oxcarbazepine added to list of drugs with increased risk of NT and other defects No other significant changes relating to pregnancy or breastfeeding
41	2001	No significant changes relating to pregnancy or breastfeeding
42	2001	4.8 Antiepileptics VALPROATE

		Advises that valproic acid (as semisodium valproate) has been recently licensed for acute mania associated with bipolar disorder. No other significant changes relating to pregnancy or breastfeeding
43	2002	Vpa migraine No other significant changes relating to pregnancy or breastfeeding
44	2002	No significant changes relating to pregnancy or breastfeeding
51	2006	No significant changes relating to pregnancy or breastfeeding
52	2006	4.8 Antiepileptics *Pregnancy and breast-feeding* – inclusion of paragraph "The concentration of antiepileptic drugs in the blood can change during pregnancy, particularly in the later stages. The dose of antiepileptics should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis." Update to paragraph: "Routine injection of vitamin K at birth effectively counteracts any antiepileptic-associated risk of neonatal haemorrhage."
53	2007	4.8 Antiepileptics *Pregnancy and breast-feeding* – lamotrigine added to the list of drugs with increased risk of neural tube and other defects.
54	2007	No significant changes relating to pregnancy or breastfeeding
55	2008	No significant changes relating to pregnancy or breastfeeding
56	2008	4.8 Antiepileptics Note – continues to give quite broad advice regarding all antiepileptics re: counselling, folate supplementation, monitoring dosage, and vitamin K injections No new information.
59	2010	General information on prescribing in pregnancy and breast-feeding is moved back to the front of the BNF. The tables removed. 4.8 Antiepileptic drugs [revised paragraphs] *Pregnancy and breast-feeding*. There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if the patient takes two or more antiepileptic drugs). However, the benefit of antiepileptic treatment usually outweighs the potential teratogenic risk, and treatment should not be stopped during pregnancy without discussing with a specialist

		(see also under individual drugs). In view of the increased risk of neural tube and other defects associated, in particular, with **carbamazepine, lamotrigine, oxcarbazepine, phenytoin,** and **valproate,** women taking antiepileptic drugs who *may become pregnant* should be **informed of the possible consequences.** Those who *wish to become pregnant* should be referred to an appropriate specialist for advice. Women who become pregnant should be **counselled** and offered **antenatal screening** (apha-fetoprotein measurement and a second trimester ultrasound scan)." Other paragraphs as before. **Sodium valproate** [new categories of information] *Pregnancy:* increased risk of congenital malformations and developmental delay if used in the first trimester (counselling and screening advised – **important:** see also Pregnancy and Breastfeeding); neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported. *Breastfeeding:* amount too small to be harmful; see also Pregnancy and Breast-feeding
60	2010	No significant changes relating to pregnancy or breastfeeding
61	2011	<u>4.8 Antiepileptic drugs</u> [revised section] *"Pregnancy.* Women of child-bearing potential should discuss the impact of both epilepsy and the treatment of epilepsy on the outcome of pregnancy with a specialist. There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of major and minor congenital malformations, and with developmental delay. Valproate should not be prescribed unless there is no safer alternative and only after a careful discussion of the risk; doses greater than 1g daily are associated with an increased risk of teratogenicity. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

		Women of child-bearing potential who take antiepileptic drugs should be given contraceptive advice. Some anti-epileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives (see…). Women who want to become pregnant should be referred to a specialist for advice in advance of conception. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester. If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose. Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a women who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern of harm to the fetus. To reduce the risk of neural tube defects, folate supplementation is advised before conception and throughout the first trimester. The concentration of antiepileptic drugs in the plasma can change during pregnancy, particularly in the later stages. Doses of phenytoin, carbamazepine and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth should be monitored. Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol, see… Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with antiepileptics. Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital." This section also includes boxed information about the Epilepsy and Pregnancy Register. *Breast-feeding* advice as before **Sodium valproate** No new information.
62	2011	4.8 Antiepileptic drugs

		Pregnancy. Inclusion of the following paragraph: "Prescribers should also consider carefully the choice of antiepileptic drugs in pre-pubescent girls who may later become pregnant." *Breast-feeding.* Updated information regarding specific risks and monitoring of infants; however advice is generally that women on AEDs should be encouraged to breast-feed. No other new information
65	2013	4.8 Antiepileptic drugs *Pregnancy* – inclusion of the following: "Topiramate carries an increased risk of cleft palate if taken in the first trimester of pregnancy." No other new information
66	2013	No significant changes relating to pregnancy or breastfeeding
67	2014	4.8 Antiepileptic drugs *Pregnancy* – update to following information on valproate: "Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and ~~with developmental delay~~ long-term neurodevelopmental effects. Valproate should not be used during pregnancy or in women of child-bearing potential ~~prescribed~~ unless there is no safer alternative and only after a careful discussion of the risk. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1g daily are associated with an increased risk of teratogenicity. Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy…" No other new information
68	2014	VALPROATE Inclusion of following paragraph "Valproate is associated with teratogenic risks – this should be fully considered and discussed before prescribing for women of child-bearing age see.." No other new information

69	2015	**Sodium valproate** [update] *Pregnancy:* avoid unless there is no safer alternative and only after a careful discussion of the risks; effective contraception advised in women of child-bearing potential; see also Pregnancy (remaining advice as before) No other new information
70	2016	**Sodium valproate** [update] *Pregnancy:* "Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy or in women of child-bearing potential unless there is no safer alternative and only after a careful discussion of the risk. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1g daily are associated with an increased risk of teratogenicity. Avoid use in the treatment of epilepsy and bipolar disorder unless there is no safer alternative and only after a careful discussion of the risks - effective contraception advised in women of child-bearing potential. Avoid use for the prophylaxis of migraine [unlicensed]- exclude pregnancy before treatment and ensure effective contraception is used during treatment. Neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported. Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. *Breast-feeding:* Present in milk – risk of haematological disorders in breast-fed new borns and infants.
71	2016	**Not located**
72	2016	<u>Epilepsy and other seizure disorders</u> *Pregnancy* – updated to include: "In the case of sodium valproate and valproic acid an urgent consultation is required to reconsider the benefits and risks of valproate therapy." No other new information
73	2017	**Sodium valproate** Includes box: "Important safety information

		MHRA/CHM advice: Valproate and risk of abnormal pregnancy outcomes. Infants exposed to valproate in utero are at a high risk of serious developmental disorders (up to 30-40% risk) and congenital malformations (approx..11% risk). Valproate should not be used in female children, females of childbearing potential or during pregnancy unless alternative treatments are ineffective or not tolerated." [new category] *Conception and contraception* – Valproate is associated with teratogenic risks and should not be used in females of child-bearing potential unless there is no safer alternative – this should be fully considered and discussed before prescribing for females of childbearing age. Exclude pregnancy before treatment – effective contraception advised in females of child-bearing potential. In females planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception. *Patient and carer advice* – contains information on risks, materials in the toolkit, and MHRA advice to prescriber on prescribing valproate to a female patient. No further new information.
74	2017	**Sodium valproate** Updated box: "MHRA/CHM ADVICE: VALPROATE AND RISK OF ABNORMAL PREGNANCY OUTCOMES Infants exposed to valproate in utero are at a high risk of serious developmental disorders (up to 30-40% risk) and congenital malformations (approx. 11% risk). Valproate should not be used in female children, females of childbearing potential or during pregnancy unless alternative treatments are ineffective or not tolerated. NHS IMPROVEMENT PATIENT SAFETY ALERT: RESOURCES TO SUPPORT THE SAFETY OF GIRLS AND WOMEN WHO ARE BEING TREATED WITH VALPROATE (APRIL 2017) The MHRA has published a set of resources, the valproate toolkit, to emphasise the need to avoid the use of valproate in girls and women of childbearing potential, warn women of the very high risk to the unborn child of valproate in pregnancy, and emphasis the need for effective contraception planning and specialist oversight of changes to medication when planning a pregnancy, as abrupt changes to medication can be harmful. All organisations providing NHS-funded care where valproate is prescribed or dispensed should undertake systematic identification of girls and women are taking valproate and ensure the MHRA resources are used to support them to make informed choices."

		No further new information Under specific indications of valproate also includes the text: "Valproate should not be used in female children, in females of childbearing potential, and pregnant females, unless alternative treatments are ineffective or not tolerated, because of its high teratogenic potential; the benefits and risks of valproate therapy should be carefully reconsidered at regular treatment reviews, see *important safety information.*
75	2018	No significant changes relating to pregnancy or breastfeeding
76	September 2018	<u>2 Epilepsy and other seizure disorders</u> *Pregnancy* – update to include specific risk and information on the PPP: "Valproate is associated with the highest risk of serious developmental disorders (up to 30-40$ risk) and congenital malformations (approx. 10% risk). Valproate must **not** be used in females of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and alternative treatments are ineffective or not tolerated; during pregnancy, it must not be used for epilepsy, unless it is the only possible treatment." Update on risks of other AEDs. **Sodium valproate** Updated box: "IMPORTANT SAFETY INFORMATION MHRA/CHM ADVICE: VALPROATE MEDICINES: CONTRA-INDICATED IN WOMEN AND GIRLS OF CHILDBEARING POTENTIAL UNLESS CONDITIONS OF PREGNANCY PREVENTION PROGRAMME ARE MET (APRIL 2018) Valproate is highly teratogenic and evidence supports that use in pregnancy leads to neurodevelopmental disorders (approx. 30-40% risk) and congenital malformations (approx. 10% risk). Valproate must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met (see *Conception and contraception)* and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist. Use of valproate in pregnancy is contra-indicated for migraine prophylaxis [unlicensed] and bipolar disorder; it must only be considered for epilepsy if there is no suitable alternative treatment (see *Pregnancy*).

		Women and girls (and their carers) must be fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy; supporting materials have been provided to use in the implementation of the Pregnancy Prevention Programme (see *Prescribing and dispensing information*). The MHRA advises that: • GPs must recall all women and girls who may be of childbearing potential, provided the Patient Guide, check they have been reviewed by a specialist in the last year and are on highly effective contraception; • Specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme, re-evaluate treatment as necessary, explain clearly the conditions as outlined in the supporting materials and complete and sign the Risk Acknowledgement Form – copies of the form must be given to the patient or carer and sent to their GP • Pharmacists must ensure valproate medicines are dispensed in whole packs whenever possible – all packs dispensed to women and girls of childbearing potential should have a warning label either on the carton or via a sticker. They must also discuss risks in pregnancy with female patients each time valproate medicines are dispenses, ensure they have the Patient Guide and have seen their GP or specialist to discuss their treatment and need for contraception. [updated sections] *Conception and contraception* – the MHRA advises that all women and girls of childbearing potential being treated with valproate medicines must be supported on a Pregnancy Prevention Programme – pregnancy should be excluded before treatment initiation and highly effective contraception must be used during treatment. *Pregnancy* – For *migraine prophylaxis* [unlicensed] and *bipolar disorder*, the MHRA advises that valproate must not be used unless there is no suitable alternative treatment; in such cases, access to counselling about the risks should be provided (see Healthcare Professional Guide for more information) and a Risk Acknowledgement Form signed by both specialist and patient. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1g daily are associated with an increased risk of teratogenicity. (continues as before) *Prescribing and dispensing information* – contains information about the PPP and associated materials. *Patient and carer advice* – includes advice that women and girls should not stop taking valproate without discussing it with their doctor.

77	March 2019	No significant changes relating to pregnancy or breastfeeding

8 NICE Guidelines

Table F.7 *Summary of NICE guidelines related to the use of antiepileptic drugs in pregnancy, and specific information about sodium valproate use.*

Date	Title	Relevant information
March 2004	Technology Appraisal 76: Newer drugs for epilepsy in adults	**1.1** Newer AEDs recommended for those who have not benefited from older AEDs or for whom they are unsuitable (e.g. interaction with oral contraceptives, women of childbearing potential). ***1.4*** *"In women of childbearing potential, the possibility of interaction with oral contraceptives and the risk of the drugs causing harm to an unborn child should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data upon which to base a definitive assessment of the risks to the unborn child associated with the newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child."* **2.12** A number of AEDs reduce the effectiveness of oral contraceptives (carbamazepine, phenytoin, barbiturates), but sodium valproate does not interfere with oral contraceptives. **2.13** "*The effects of these drugs on the unborn child are also a matter for concern. All the older antiepileptic drugs have been associated with malformations (see Section 4.1.15). Multiple drug therapy is associated with a greater risk, although this may be related to the severity of the mother's epilepsy. The Summary of Product Characteristics for sodium valproate (Epilim) recommends that women of childbearing potential should not be started on sodium valproate without specialist neurological advice, and that for partial seizures sodium valproate should be used only in women found to be resistant to other treatments.*"

		4.1.15 *Few data are available on the use of newer antiepileptic drugs in pregnancy, and it is not yet possible to fully assess the risk of teratogenicity associated with them. Preliminary data from the UK Epilepsy and Pregnancy Register presented in 2002 (based on the outcomes of 2028 pregnancies) suggest that the crude rates for risk of major congenital malformation were 4% (95% confidence interval [CI] 3.2% to 5.3%) in women taking one antiepileptic drug and 6.3% (95% CI, 4.3% to 9.1%) in women taking more than one. There are also data for a small group of women with epilepsy (5.9% of the total) who were not exposed to antiepileptic drugs during pregnancy. The crude malformation rate in this group was 0.9% (95% CI, 0.2% to 4.7%). For the older drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), and the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%). The risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%), but no risks were reported for any of the other newer agents. These data suggest that sodium valproate is associated with a statistically significantly higher risk of malformations than carbamazepine. Although the crude rate for lamotrigine was lower than for sodium valproate, the difference was not statistically significant.* ***4.3.2*** *The Committee considered that the evidence from randomised trials comparing newer and older antiepileptic drugs as monotherapy did not suggest differences in their effectiveness in seizure control. There was also insufficient evidence to distinguish between the different newer antiepileptic drugs for seizure control. Although side-effect profiles of the drugs were different, the Committee considered that the evidence was inadequate to support a conclusion that the newer drugs were generally associated with improved quality of life. The integrated cost effectiveness analysis showed a high degree of uncertainty around the costs and benefits of these treatments. Thus, given the higher cost of the newer antiepileptic drugs, the Committee recommended that first-line monotherapy should be initiated with one of the older antiepileptic drugs, such as carbamazepine or sodium valproate, unless these drugs are not suitable because there are contra-indications or the potential for interactions with other drugs the person is taking, because they have been poorly tolerated by the person in the past, or because the person is a woman of childbearing potential.* ***4.3.8*** *The Committee noted that the issue of whether antiepileptic drugs may be harmful to the unborn child if taken during pregnancy is a major concern. The Committee specifically took note of the particular concern regarding the risks to the unborn child associated with the use of sodium valproate and that, because of this, the Summary of Product Characteristics for sodium valproate (Epilim) warns that, for partial seizures, sodium valproate should be used in women only if they are*

		resistant to other treatments. The experts advised the Committee that despite the concerns highlighted in the Summary of Product Characteristics, sodium valproate may be an appropriate choice for women of childbearing age with some types of generalised seizures, provided that an informed choice has been made. The Committee was persuaded that, as yet, there are few data upon which to base a robust assessment of the risks to the unborn child associated with newer drugs. ***4.3.9*** *Additionally, the Committee took note of the potential for drug interactions with the use of the antiepileptic drugs and, in particular, interactions with oral contraceptives, which may be of relevance in women of childbearing potential. It concluded that this aspect of therapy should be taken into account in determining the most suitable treatment for any individual.* ***5*** *Recommendations for further research* ***5.1*** *A large randomised controlled trial of longer-term clinical outcomes and cost effectiveness of standard and new antiepileptic drugs (SANAD) has been sponsored by the NHS R&D Health Technology Assessment Programme. The study aims to recruit about 3000 people in the UK over 3 years. The study will compare monotherapy with clinicians' first-choice standard drug (carbamazepine or sodium valproate) with appropriate comparators from among the new antiepileptic drugs. This study will be the largest randomised controlled trial in epilepsy and is intended to provide robust evidence for the effectiveness of the newer antiepileptic drugs.* ***7.3.4*** *In women of childbearing potential, the risk of the drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives are discussed between the woman and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.* Appendix C – Criteria for an audit, possible criterion should include woman of childbearing potential; The risk of the antiepileptic drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives are discussed with a woman of childbearing potential

April 2004	Technology Appraisal 79: Newer drugs for epilepsy in children	**1.1** Newer AEDs recommended for those who have not benefited from older AEDs or for whom they are unsuitable (e.g. interaction with oral contraceptives, girl childbearing potential or likely to need treatment into childbearing years). **1.*5*** *In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs causing harm to an unborn child, and the possibility of interaction with oral contraceptives, should be discussed with the child and/or their carer, and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.* ***2.19*** *The most commonly prescribed antiepileptic drugs in the UK are sodium valproate and carbamazepine. Phenytoin is also still widely used. Carbamazepine is licensed for the treatment of partial seizures and generalised tonic–clonic seizures and is used as a first-line option in these types of seizure. Sodium valproate is a broad-spectrum antiepileptic drug that is licensed for the complete range of seizure types. It is used as a first-line option in primary generalised seizures, absence and myoclonic seizures, and may be tried in atypical absence, atonic and tonic seizures. Phenytoin is licensed for tonic–clonic seizures, partial seizures, or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.* ***2.22*** *The older antiepileptic drugs have the potential to interact with numerous drugs. Sodium valproate is a hepatic enzyme inhibitor. This means that it slows the metabolism of drugs that are metabolised by these enzymes so dose reduction may be needed to avoid toxicity. Carbamazepine, phenytoin and barbiturates induce hepatic enzymes. This means that they can accelerate the metabolism of some drugs (including oral contraceptives), and higher doses will be needed or the drugs will be less effective. The influence of antiepileptic drug selection on current or future choices of contraceptive methods needs to be borne in mind when choosing an antiepileptic drug for girls who are likely to continue treatment into their childbearing years.*

		2.23 *The effects of antiepileptic drugs on the unborn child are also a matter for concern when selecting treatment for girls who are likely to need to continue treatment into their childbearing years. All the older antiepileptic drugs have been associated with congenital malformations (see Section 4.1.7). Multiple drug therapy is associated with a greater risk, although this may be related to the severity of the mother's epilepsy. The Summary of Product Characteristics for sodium valproate (Epilim) recommends that women of childbearing potential should not be started on sodium valproate without specialist neurological advice and that, for partial seizures, sodium valproate should be used only in women found to be resistant to other treatments.* ***4.1.7 Newer antiepileptic drugs and childbearing potential*** *4.1.7.1 In selecting antiepileptic drugs for girls who are likely to need continued treatment into adulthood, safety in pregnancy needs to be considered. Few data are available on the use of newer antiepileptic drugs in pregnancy, and it is not yet possible to fully assess the risk of teratogenicity associated with them. Preliminary data from the UK Epilepsy and Pregnancy Register presented in 2002 (based on the outcomes of 2028 pregnancies) suggest that the crude rates for risk of major congenital malformation were 4% (95% confidence interval [CI], 3.2% to 5.3%) in women taking one antiepileptic drug and 6.3% (95% CI, 4.3% to 9.1%) in women taking more than one. There are also data for a small group of women with epilepsy (5.9% of the total) who were not exposed to antiepileptic drugs during pregnancy. The crude malformation rate in this group was 0.9% (95% CI, 0.2% to 4.7%). For the individual drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%) and the risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%). These data suggest that sodium valproate is associated with a significantly higher risk of malformations than carbamazepine. Although the crude rate for lamotrigine was lower than for sodium valproate, the difference was not statistically significant.* 4.3.6 The experts and patient representatives stressed that the most important outcome for people with epilepsy is seizure freedom. ***4.3.12*** *The Committee noted that the issue of whether antiepileptic drugs may be harmful to the unborn child is a matter of major concern and should be considered in the treatment of girls of childbearing potential (and younger girls who are likely*

		to need continued treatment into adolescence and adulthood). The Committee took specific note of the particular concern regarding the risks to the unborn child associated with sodium valproate and that, because of this, the Summary of Product Characteristics for sodium valproate (Epilim) warns that, for partial seizures, it should be used in women and girls only if they are resistant to other treatments. The experts advised the Committee that despite the concerns highlighted in the Summary of Product Characteristics, sodium valproate may be an appropriate choice for women or girls with some types of generalised seizures. However, when considering the use of sodium valproate in girls of childbearing potential, the risks and benefits must be clearly communicated with both the child and her carer as appropriate to ensure that an informed choice is made. The Committee were persuaded that, as yet, there are few data upon which to base an assessment of the potential risks of teratogenicity associated with newer drugs. ***4.3.13*** *Additionally, the Committee took note of the potential for drug interactions with the use of the antiepileptic drugs and, in particular, interaction with oral contraceptives, which may be of relevance in girls of childbearing potential. They concluded that this aspect of therapy should be taken into account in determining the most suitable treatment for any individual patient.* ***5 Recommendations for further research*** ***5.1*** *A large randomised controlled trial of longer-term clinical outcomes and cost effectiveness of standard and new antiepileptic drugs (SANAD) has been sponsored by the NHS R&D Health Technology Assessment Programme. The study aims to recruit around 3000 people in the UK over 3 years. The study will compare monotherapy with clinicians' firstchoice standard drug (carbamazepine or sodium valproate) with appropriate comparators from among the new antiepileptic drugs. Both adults and children of 5 years or older will be included. This study will be the largest randomised controlled trial in epilepsy and is intended to provide robust evidence for the effectiveness of the newer antiepileptic drugs.* ***7.3.5*** *In girls of childbearing age, the risk of the drugs causing harm to an unborn child is discussed between the girl and/or her carer and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.*

		Appendix C – Measures that could be used as a basis for audit. Include: meeting criteria to be treated with newer antiepileptic drug if of childbearing potential or is likely to need treatment into childbearing years; In girls of childbearing age, the risk of the drugs causing harm to an unborn child is discussed between the girl and/or her carer and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs
October 2004	Clinical Guideline 20: The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care	**Key priorities for implementation** ***(p6)*** *The AED (anti-epileptic drug) treatment strategy should be individualised according to the seizure type, epilepsy syndrome, comedication and co-morbidity, the individual's lifestyle, and the preferences of the individual, their family and/or carers as appropriate.* ***(p7) Special considerations for women of childbearing potential for further assessment.*** *Women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children, breastfeeding and menopause.* 1.3.1 Individuals with epilepsy and their families and/or carers should be given, and have access to sources of, information about (where appropriate): [list includes] family planning and pregnancy 1.3.10 People with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). 1.8.3 Epilepsy specialist nurses (ESNs) should be an integral part of the network of care of individuals with epilepsy. The key roles of the ESNs are to support both epilepsy specialists and generalists, to ensure access to community and multi-agency services and to provide information, training and support to the individual, families, carers and, in the case of children, others involved in the child's education, welfare and well-being. 1.8.4 Healthcare professionals have a responsibility to educate others about epilepsy so as to reduce the stigma associated with it. They should provide information about epilepsy to all people who come into contact with people with epilepsy, including school staff, social care professionals and others.

1.8.27 Indications for monitoring of AED blood levels are: [includes] pregnancy

1.11 Women with epilepsy

1.11.1 In order to enable informed decisions and choice, and to reduce misunderstandings, women with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause.

1.11.2 Information about contraception, conception, pregnancy, or menopause should be given to girls and women in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with girls and women with epilepsy. These may include an individual's family and/or carers.

1.11.3 All healthcare professionals who treat, care for, or support women with epilepsy should be familiar with relevant information and the availability of counselling.

1.11.4 A In women of childbearing potential, the risk of the drugs (see 1.8.13A) causing harm to an unborn child should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child. (NICE)	**1.11.4**C In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs (see 1.8.13C) causing harm to an unborn child should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child. (NICE)

1.11.5 Prescribers should be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of childbearing potential.

1.11.6 All women on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy.

Contraception

1.11.7 A In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. (NICE)	1.11.7C In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the possibility of interaction with oral contraceptives should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. (NICE)

1.11.8 In women of childbearing potential, the risks and benefits of different contraceptive methods, including hormone-releasing IUDs, should be discussed.

1.11.9 If a woman taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, a minimum initial dose of 50 micrograms of oestrogen is recommended. If breakthrough bleeding occurs, the dose of oestrogen should be increased to 75 micrograms or 100 micrograms per day, and 'tricycling' (taking three packs without a break) should be considered.

1.11.10 The progesterone-only pill is not recommended as reliable contraception in women taking enzyme-inducing AEDs.

1.11.11 Women taking enzyme-inducing AEDs who choose to use depot injections of progesterone should be informed that a shorter repeat injection interval is recommended (10 weeks instead of 12 weeks).

		1.11.12 The progesterone implant is not recommended in women taking enzyme-inducing AEDs. 1.11.13 The use of additional barrier methods should be discussed with women taking enzyme-inducing AEDs and oral contraception or having depot injections of progesterone. 1.11.14 If emergency contraception is required for women taking enzyme inducing AEDs, the dose of levonorgestrel should be increased to 1.5 mg and 750 micrograms 12 hours apart. **Pregnancy** 1.11.15 Women with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women who plan to stop AED therapy (see Sections 1.8.30–1.8.35). 1.11.16 All pregnant women with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to the UK Epilepsy and Pregnancy Register (www.epilepsyandpregnancy.co.uk). 1.11.17 In all women with epilepsy, seizure freedom during pregnancy should be sought. 1.11.18 The clinician should discuss with the woman the relative benefits and risks of adjusting medication to enable her to make an informed decision. Where appropriate, the woman's specialist should be consulted. 1.11.19 Women with generalised tonic–clonic seizures should be informed that the fetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency. 1.11.20 Women should be reassured that there is no evidence that simple partial, complex partial, absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury.

		1.11.21 Women should be reassured that an increase in seizure frequency is generally unlikely in pregnancy or in the first few months after birth. 1.11.22 Generally, women may be reassured that the risk of a tonic–clonic seizure during the labour and the 24 hours after birth is low (1– 4%). 1.11.23 Routine monitoring of AED levels in pregnancy is not recommended. If seizures increase, or are likely to increase, monitoring of AED levels may be useful to plan or anticipate the extent of change of dose adjustment needed. 1.11.24 Women with epilepsy should be informed that although they are likely to have healthy pregnancies, their risk of complications during pregnancy and labour is higher than for women without epilepsy. 1.11.25 Care of pregnant women should be shared between the obstetrician and the specialist. 1.11.26 Pregnant women who are taking AEDs should be offered a high resolution ultrasound scan to screen for structural anomalies. This scan should be performed at 18–20 weeks' gestation by an appropriately trained ultrasonographer, but earlier scanning may allow major malformations to be detected sooner. 1.11.27 The risk of seizures during labour is low, but it is sufficient to warrant the recommendation that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures. 1.11.28 All children born to mothers taking enzyme-inducing AEDs should be given 1 mg of vitamin K parenterally at delivery. 1.11.29 Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has idiopathic epilepsy and a positive family history of epilepsy.

		1.11.30 Although there is an increased risk of seizures in children of parents with epilepsy, individuals with epilepsy should be given information that the probability that a child will be affected is generally low. However, this will depend on the family history. 1.11.31 Advanced planning, including the development of local protocols for care, should be implemented in obstetric units that deliver babies of women with epilepsy. 1.11.32 Joint epilepsy and obstetric clinics may be convenient for mothers and healthare professionals but there is insufficient evidence to recommend their routine use. 1.11.33 It is, however, important that there should be regular follow-up, planning of delivery, and liaison between the specialist or epilepsy team and the obstetrician or midwife. **Breastfeeding** 1.11.34 All women with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. 1.11.35 Prescribers should consult Appendix 5 of the British National Formulary when prescribing AEDs for women who are breastfeeding. The decision on whether to continue AED therapy should be made between the woman and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. **After the birth** 1.11.36 Parents of new babies or young children should be informed that introducing a few simple safety precautions may significantly reduce the risk of accidents and minimise anxiety. An approaching birth can be an ideal opportunity to review and consider the best and most helpful measures to start to ensure maximum safety for both mother and baby. GPP

1.11.37 Information should be given to all parents about safety precautions to be taken when caring for the baby (see Appendix D of the full guideline).

1.11.38 Parents should be reassured that the risk of injury to the infant caused by maternal seizure is low.

1.16 Review

1.16.1 Adults and children with epilepsy should have a regular structured review and be registered with a general medical practice.

1.16.5 A Adults with well controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist.

4 Research recommendations

- Large, population-based studies on rates of misdiagnosis
- Economic evaluations of cost-effectiveness of diagnosis methods, and evaluation of particular methods
- Large, population-based studies on prognosis in children
- RCTs on use of epilepsy specialist nurses, and epilepsy clinics
- Qualitative studies including risk communication, experiences of BAME individuals, experiences of individuals with learning disabilities, information needs
- A large RCT of longer-term clinical outcomes and cost-effectiveness of standard and new antiepileptic drugs (SANAD) has been sponsored by the NHS R&D Health Technology Appraisal Programme. The study will compare monotherapy with clinicians' first-choice standard drug with appropriate comparators from the newer AEDs.

Appendix Table 4 Side effects of drug treatment in adults that may be clinically significant GPP

Sodium valproate only drug with fetal malformation as listed side effect

Sodium valproate	odium valproate has been associated with amenorrhoea and irregular periods. Any menstrual problems should be reported to the GP and

			neurologist. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.
January 2012	CG 137 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care	(p7) *Newer and more expensive AEDs are now being prescribed, and with an increase in treatment costs likely in coming years it is essential to ensure that AEDs with proven clinical and cost effectiveness are identified. The evidence used to develop The epilepsies (NICE clinical guideline 20), Newer drugs for epilepsy in adults (NICE technology appraisal guidance 76) and Newer drugs for epilepsy in children (NICE technology appraisal guidance 79) showed no difference in effectiveness between newer and older AEDs, or between the newer drugs (as monotherapy) for seizure control. However, a recent large multicentre trial (the SANAD trial) evaluating newer drugs in newly diagnosed epilepsy (accepting some limitations) suggested that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in focal epilepsies. It was therefore considered necessary to review new evidence regarding AEDs within an update of NICE clinical guideline 20 (which was published in 2004).* **(p11) Special considerations for women and girls of childbearing potential** Women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children, breastfeeding and menopause. [2004] 1.3 Information 1.3.1 Children, young people and adults with epilepsy and their families and/or carers should be given, and have access to sources of, information about (where appropriate): [including] family planning and pregnancy **1.9 Pharmacological treatment** The GDG is also aware of specific issues with prescribing sodium valproate to girls and women of childbearing age. Recommendations in this section offer alternative prescribing options for this group. Recommendations 1.9.1.10, 1.9.17.3, 1.9.17.6, 1.9.17.9 and 1.15.1.4 also provide additional specific information of relevance when considering prescribing AEDs to women of childbearing age.	

		1.9.1.10When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. [new 2012] This section contains specific guidance on treatment of different epilepsy types, noting that prescribers should be aware of the teratogenic risks of sodium valproate. Sodium valproate is recommended as a first line treatment in : - children, young people and adults with newly diagnosed generalised tonic–clonic (GTC) seizures - children, young people and adults with absence seizures - children, young people and adults with myoclonic seizures - children, young people and adults with tonic or atonic seizures - children with Dravet syndrome - children with Lennox–Gastaut syndrome - children, young people and adults with idiopathic generalised epilepsy (IGE) - children, young people and adults with juvenile myoclonic epilepsy (JME) - children, young people and adults with epilepsy with GTC seizures only - children, young people and adults with childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes As alternatives if the first line treatment is ineffective but not tolerated in : - children, young people and adults with newly diagnosed focal seizures - children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) Also recommends sodium valproate as adjunctive treatment if first-line treatment is not effective. 1.9.17.9Indications for monitoring of AED blood levels are: [includes] certain situations in pregnancy (see recommendation 1.15.3.19). [2012] **1.15 Women and girls with epilepsy** **1.15.1 Information and advice for women and girls with epilepsy**

		1.15.1.1In order to enable informed decisions and choice, and to reduce misunderstandings, women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause. [2004] 1.15.1.2Information about contraception, conception, pregnancy, or menopause should be given to women and girls in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with women and girls with epilepsy. These may include her family and/ or carers. [2004] 1.15.1.3All healthcare professionals who treat, care for, or support women and girls with epilepsy should be familiar with relevant information and the availability of counselling. [2004] 1.15.1.4Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. [new 2012] 1.15.1.5Be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of present and future childbearing potential. [2012] 1.15.1.6All women and girls on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. [2004] 1.15.1.7Refer to the SPC and BNF (available at http://bnf.org) for individual drug advice on the interactions between AEDs and hormonal replacement and contraception. [new 2012]

		1.15.2 Contraception 1.15.2.1In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. [2004] 1.15.2.2In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the possibility of interaction with oral contraceptives should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. [2004] 1.15.2.3In women and girls of childbearing potential, the risks and benefits of different contraceptive methods, including hormone-releasing IUDs, should be discussed. [2004] 1.15.2.4If a woman or girl taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, guidance about dosage should be sought from the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012] 1.15.2.5The progestogen[21] -only pill is not recommended as reliable contraception in women and girls taking enzyme-inducing AEDs. [2004, amended 2012] 1.15.2.6The progestogen[20] implant is not recommended in women and girls taking enzyme-inducing AEDs. [2004, amended 2012] 1.15.2.7The use of additional barrier methods should be discussed with women and girls taking enzyme-inducing AEDs and oral contraception or having depot injections of progestogen. [2004, amended 2012]

		1.15.2.8If emergency contraception is required for women and girls taking enzymeinducing AEDs, the type and dose of emergency contraception should be in line with the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012] 1.15.2.9Discuss with women and girls who are taking lamotrigine that the simultaneous use of any oestrogen-based contraceptive can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When a woman or girl starts or stops taking these contraceptives, the dose of lamotrigine may need to be adjusted. [new 2012] **1.15.3 Pregnancy** 1.15.3.1Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women and girls who plan to stop AED therapy (see section 1.9.18). [2004] 1.15.3.2All pregnant women and girls with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to the UK Epilepsy and Pregnancy Register (www.epilepsyandpregnancy.co.uk). [2004] 1.15.3.3The clinician should discuss with the woman and girl the relative benefits and risks of adjusting medication to enable her to make an informed decision. Where appropriate, the woman or girl's specialist should be consulted. [2004] 1.15.3.4Women and girls with generalised tonic–clonic seizures should be informed that the fetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency. [2004] 1.15.3.5Women and girls should be reassured that there is no evidence that focal[17 absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury. [2004, amended 2012]

		1.15.3.6Women and girls should be reassured that an increase in seizure frequency is generally unlikely in pregnancy or in the first few months after birth. [2004] 1.15.3.7Generally, women and girls may be reassured that the risk of a tonic–clonic seizure during the labour and the 24 hours after birth is low (1–4%). [2004] 1.15.3.8Women and girls with epilepsy should be informed that although they are likely to have healthy pregnancies, their risk of complications during pregnancy and labour is higher than for women and girls without epilepsy. [2004] 1.15.3.9Care of pregnant women and girls should be shared between the obstetrician and the specialist. [2004] 1.15.3.10Pregnant women and girls who are taking AEDs should be offered a high-resolution ultrasound scan to screen for structural anomalies. This scan should be performed at 18–20 weeks' gestation by an appropriately trained ultra-sonographer, but earlier scanning may allow major malformations to be detected sooner. [2004] 1.15.3.11The risk of seizures during labour is low, but it is sufficient to warrant the recommendation that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures. [2004] 1.15.3.12All children born to mothers taking enzyme-inducing AEDs should be given 1 mg of vitamin K parenterally at delivery. [2004] 1.15.3.13Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has idiopathic epilepsy and a positive family history of epilepsy. [2004]

		1.15.3.14Although there is an increased risk of seizures in children of parents with epilepsy, children, young people and adults with epilepsy should be given information that the probability that a child will be affected is generally low. However, this will depend on the family history. [2004] 1.15.3.15Advanced planning, including the development of local protocols for care, should be implemented in obstetric units that deliver babies of women and girls with epilepsy. [2004] 1.15.3.16Joint epilepsy and obstetric clinics may be convenient for mothers and healthcare professionals but there is insufficient evidence to recommend their routine use. [2004] 1.15.3.17It is, however, important that there should be regular follow-up, planning of delivery, and liaison between the specialist or epilepsy team and the obstetrician or midwife. [2004] 1.15.3.18Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalised tonic–clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of each AED, avoiding polytherapy if possible. [new 2012] 1.15.3.19Do not routinely monitor AED levels during pregnancy. If seizures increase or are likely to increase, monitoring AED levels (particularly levels of lamotrigine and phenytoin, which may be particularly affected in pregnancy) may be useful when making dose adjustments. [new 2012] **1.15.4 Breastfeeding** 1.15.4.1All women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women and girls taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. [2004]

		1.15.4.2Prescribers should consult individual drug advice in the SPC and the BNF (available at http://bnf.org)[22] when prescribing AEDs for women and girls who are breastfeeding. The decision regarding AED therapy and breastfeeding should be made between the woman or girl and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. [2004, amended 2012] **1.15.5 After the birth** 1.15.5.1Parents of new babies or young children should be informed that introducing a few simple safety precautions may significantly reduce the risk of accidents and minimise anxiety. An approaching birth can be an ideal opportunity to review and consider the best and most helpful measures to start to ensure maximum safety for both mother and baby. [2004] 1.15.5.2Information should be given to all parents about safety precautions to be taken when caring for the baby (see appendix D[23] of the full guideline). [2004] 1.15.5.3Parents should be reassured that the risk of injury to the infant caused by maternal seizure is low. [2004] **Review** **1.20.7** Adults with well-controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist. [2004] Research recommendations include: - Comparison of efficacy of newer AEDs and standard AEDs - Initial and add-on treatment in childhood-onset epilepsy syndromes - Treatment outcomes in infantile spasms - Safety and efficacy of treatment for convulsive status epilepticus - **4.5 AEDs and pregnancy:** What is the malformation rate and longer term neurodevelopmental outcome of children born to mothers who have taken AEDs during pregnancy? -

February 2014	Evidence Update 53: A summary of selected new evidence relevant to NICE clinical guideline 137 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' (2012)	Number of topics for update, including: **Women and girls with epilepsy** **In utero exposure to AEDs and risk of congenital malformations** Among women who take AEDs, particularly sodium valproate, during pregnancy, those who have children with congenital abnormalities are at higher risk of having fetal malformations in subsequent pregnancies exposed to AEDs than women whose first pregnancies did not result in fetal malformations. **In utero exposure to AEDs and cognitive outcome** Limited evidence suggests that compared with other AEDs, sodium valproate during pregnancy has a negative, dose-dependent effect on long-term cognitive outcomes in offspring. Periconceptional folic acid may lessen the effect of AED use during pregnancy on the child's intelligence quotient (IQ). **Breastfeeding** Limited evidence suggests that AED use while breastfeeding does not affect cognitive outcome in children exposed to AEDs in utero. 1.15 Women and girls with epilepsy **Information and advice for women and girls with epilepsy** NICE CG137 recommends discussing with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Specifically, the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk, should be discussed. The MHRA has issued a special reminder on the risk of neurodevelopmental delay in children following maternal use of sodium valproate. The agency states that sodium valproate should not be used during pregnancy and in women of childbearing potential unless there is no effective alternative. Women of childbearing potential should not start treatment

		with sodium valproate without specialist neurological or psychiatric advice, as appropriate depending on the indication. Adequate counselling should be made available to all women of childbearing potential to weigh the risk of teratogenic and neurodevelopmental effects against the benefits of treatment. The risks and benefits of treatment with individual drugs should be assessed. Limited data are available on risks to the unborn child associated with newer drugs. Healthcare professionals should be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of present and future childbearing potential. All pregnant women and girls with epilepsy should be encouraged to notify their pregnancy, or allow their clinician to notify the pregnancy, to the UK Epilepsy and Pregnancy Register, which prospectively collects clinical data from pregnant women with epilepsy who are on 1 or more AEDs. **In utero exposure to AEDs and risk of congenital malformations** Two registry studies, 1 using data from Australia and the other from the UK, provide evidence on the risk of women taking AEDs, who have had 1 birth with congenital abnormalities, having malformations in subsequent offspring. Vajda et al. (2013) analysed data collected by the Australian Register of Antiepileptic Drugs in Pregnancy between 1999 and 2010. The registry prospectively and retrospectively collected information on pregnant women who took AEDs throughout pregnancy, either for epilepsy or disorders other than epilepsy, and on women with epilepsy who did not take AEDs at least in the first trimester of pregnancy. Information from the end of the first postnatal month and the first postnatal year was used to determine the presence of fetal abnormalities. The first pregnancy enrolled by a woman on the register was considered to be the 'index' pregnancy (even among those women who had previously had pregnancies). Data on the index pregnancy were available for 1243 women enrolling on the register (all but 37 of whom had epilepsy). For 647 of these women, the index pregnancy was their first pregnancy. The remaining 596 women reported having already had at least 1 pregnancy before enrolling. After enrolment, 228 women went on to have a second pregnancy – 45 of whom subsequently had further pregnancies. Overall, a total of 2637 pregnancies were recorded, 1114 of which took place before the index pregnancy.

		In the index pregnancies, women who took sodium valproate during the first trimester of pregnancy (n=337) were more likely than those took other AEDs (n=789) to have a pregnancy with congenital abnormalities (13.1% versus 4.4%, OR 3.24, 95% CI 2.03 to 5.15). The rate of abnormalities in pregnancies exposed to AEDs other than sodium valproate was not appreciably different from the rate when no AEDs were involved (4.4% versus 4.3%). Women whose index pregnancy had resulted in an AED-related fetal abnormality were significantly more likely to have a fetal malformation in their next pregnancy than were women whose index pregnancy was normal despite AED treatment (35.7% versus 3.1%, OR=17.6, 95% CI 4.5 to 68.7). This higher rate of fetal malformations was not significant in the subgroup of women taking AEDs other than sodium valproate during each pregnancy (14.3% versus 1.96%, OR=8.33, 95% CI 0.75 to 92.4) but was significant in those on sodium valproate (57.1% versus 7.0%, OR=17.8, 95% CI 2.7 to 119.1). Spontaneous or induced abortions had occurred in 264 (44.3%) of the pre-index pregnancies in women who had been pregnant at least once before enrolment. In the remaining 332 pregnancies, congenital abnormalities had occurred in 4 (2.8%) of the 145 pregnancies not exposed to AEDs, 12 (10.1%) of the 119 pregnancies exposed to AEDs other than sodium valproate (OR versus unexposed pregnancies 3.95, 95% CI 1.24 to 12.6) and 11 (16.2%) of the 68 pregnancies exposed to sodium valproate (OR versus unexposed pregnancies 6.80, 95% CI 2.08 to 22.2). However, the difference in rates between pregnancies exposed to sodium valproate and those exposed to AEDs other than sodium valproate was not significant (OR 1.72, 95% CI 0.71 to 4.14). Campbell et al. (2013) analysed data from the UK Epilepsy and Pregnancy Register. Outcomes were reviewed for women registered between 1996 and 2011 who had 2 or more pregnancies that resulted in a live birth, or a pregnancy loss that had a congenital malformation. The primary outcome was the risk of major or minor congenital malformations. The analysis comprised 1371 singleton pregnancies in 646 women. In total 83 (12.8%) women had a congenital abnormality in their first pregnancy, 14 of whom had at least 1 more child with a congenital abnormality (recurrence rate=16.9%). Among the 563 women who did not have a congenital abnormality in their first pregnancy, 55 (9.8%) subsequently had a child with a congenital abnormality. Women whose first child had a

		congenital abnormality were more likely to have a congenital abnormality in a subsequent pregnancy than women whose first child was not malformed (RR=1.73, 95% CI 1.01 to 2.96, p=0.04). The recurrence rates by AED type did not differ significantly, but this finding may have been because the numbers of pregnancies exposed to each AED were small. Limitations of Vajda et al. (2013) included that the data on previous pregnancies were selfreported by the women in the study; therefore, the retrospective information may be less reliable than the prospective information. Campbell et al. (2013) also used self-reporting to collect data, as well as reporting by healthcare professionals. Both studies were observational, so residual confounding by baseline characteristics is possible. Campbell et al. (2013) had a short period after birth in which fetal malformations could be identified (up to 6 weeks) and was limited by the small number of events. The evidence suggests that among women who take AEDs, particularly sodium valproate, during pregnancy, those who have children with congenital abnormalities are at higher risk of having fetal malformations in subsequent pregnancies exposed to AEDs than women whose first pregnancies did not result in fetal malformations. The risk of recurrent abnormalities highlighted in this evidence is consistent with the recommendations in NICE CG137 that sodium valproate is associated with a particularly high risk to the unborn child. *Key references* *Campbell E, Devenney E, Morrow J et al. (2013) Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. Epilepsia 54: 165–71* *Vajda FJ, O'Brien TJ, Lander CM et al. (2013) Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. Epilepsia 54: 181–6* **In utero exposure to AEDs and cognitive outcome** An observational, single-blind study at 25 centres in the UK and the USA by Meador et al. (2013) assessed the effects of AED use during pregnancy on cognitive outcomes in children. This paper reports findings from the Neurodevelopmental Effects of Antiepileptic Drugs study of pregnant women with epilepsy on AED monotherapy (carbamazepine, lamotrigine,

		phenytoin or sodium valproate). Assessors blinded to treatment evaluated the cognitive development of these women's offspring at 2, 3, 4.5 and 6 years. The primary analysis included 311 live births in 305 mothers. Cognitive outcomes were available from at least 1 of the 4 test ages for 279 (90%) children; 224 children completed 6 years of follow-up. Analysis was adjusted for maternal intelligence quotient (IQ), AED type, AED standardised dose, gestational age at birth and use of periconceptional folate. Children exposed to sodium valproate in utero had significantly lower IQ scores at 6 years (mean IQ=97, 95% CI 94 to 101) than those exposed to carbamazepine (mean IQ=105, 95% CI 102 to 108, p=0.0015), phenytoin (mean IQ=108, 95% CI 104 to 112, p=0.0006) or lamotrigine (mean IQ=108, 95% CI 105 to 110, p=0.0003). The negative effect of sodium valproate on IQ worsened with increasing dose (r=−0.56, p<0.001), and was most marked on verbal functioning and memory. IQ at 6 years was higher in children whose mothers used periconceptional folic acid (mean IQ=108, 95% CI 106 to 111) than in those whose mothers did not take folic acid (mean IQ=101, 95% CI 98 to 104, p=0.0009). Limitations of the evidence included that the sample was relatively small (n=311), a large proportion of participants was lost to 6-year follow-up (28%), no unexposed controls were included and the maternal folic acid data was established retrospectively by self-report. Limited evidence suggests that compared with other AEDs, sodium valproate during pregnancy has a negative, dose-dependent effect on long-term cognitive outcomes in offspring. Periconceptional folic acid may lessen the effect of AED use during pregnancy on the child's IQ. The evidence is consistent with the recommendation in NICE CG137 that sodium valproate, particularly doses of more than 800 mg/day, is associated with a greater risk to the unborn child. The evidence is also consistent with the recommendation that all women and girls on AEDs should be offered 5 mg/day of folic acid before any possibility of pregnancy. Registry studies give limited information, so further research is needed to confirm these findings and data on more AEDs are required. *Key reference*

		Meador KJ, Baker GA, Browning N et al. (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 12: 244– 52 [NIH Public Access author manuscript – full text] **Breastfeeding** NICE CG137 recommends that all women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding is generally safe for most women and girls taking AEDs and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. The guidance recommends that prescribers should consult individual drug advice in the summary of product characteristics and the British national formulary when prescribing AEDs for women and girls who are breastfeeding. The decision regarding AED therapy and breastfeeding should be made between the woman or girl and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. A second paper using data from the Neurodevelopmental Effects of Antiepileptic Drugs study by Meador et al. (2010) investigated the effects of breastfeeding during AED therapy on the cognitive outcomes of offspring. The study enrolled pregnant women with epilepsy in the UK and USA who were taking AED monotherapy (carbamazepine, lamotrigine, phenytoin or sodium valproate) during pregnancy. Participants were followed up by telephone at 3 months after delivery to check whether they were breastfeeding. Assessors blinded to AED evaluated cognitive outcomes in offspring at 36–45 months old using the Differential Ability Scales. The primary analysis comprised 194 women and 199 children (5 sets of twins) for whom data on breastfeeding and cognitive outcome at 3 years were available. Overall, 84 (42%) children were breastfed for a median of 6 months (range 3–24 months). The mean adjusted IQ score at 3 years was 99 (95% CI 96 to 103) in all breastfed children and 98 (95% CI 95 to 101) in children who were not breastfed (p=0.49). Maternal IQ was the variable most strongly associated with child IQ (p=0.0001), followed by gestational age (p=0.005), maternal age and folic acid use around conception (p=0.01 for both). AED type had a weaker association (p=0.04), but AED dose was not associated with child IQ (p=0.05)

		This study is limited by the lack of any data on the amount of breastfeeding. In addition, the study had a relatively small sample size (n=199 children), was not randomised and did not include children who were not exposed to AEDs during pregnancy but subsequently exposed during breastfeeding. The study was powered to detect a 0.5 standard deviation effect on IQ in the combined analysis of all AEDs (a clinically meaningful difference) but not for analysis of individual AEDs, so was not able to determine the effects of particular AEDs on IQ. Limited evidence suggests that AED use while breastfeeding does not affect cognitive outcome in children exposed to AEDs in utero. This finding is consistent with the advice in NICE CG137 that breastfeeding is generally safe for most women and girls taking AEDs and should be encouraged. *Key reference* *Meador KJ, Baker GA, Browning N et al. (2010) Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 75: 1954–60*
January 2015	CG127 – Update on website	*The Medicines and Healthcare Products Regulatory Agency (MHRA) has strengthened its warnings on the use of valproate in women of childbearing potential. We are assessing the impact of this on the guideline. In the meantime, healthcare professionals are advised to use the guideline in conjunction with the latest MHRA advice.*
February 2016	CG127 – Update on website	*The Medicines and Healthcare Products Regulatory Agency (MHRA) has produced a toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy (http://www.gov.uk/government/publications/toolkit-on-therisks-of-valproate-medicines-in-female-patients). Healthcare professionals are advised to use the NICE guideline in conjunction with the latest MHRA advice and resources. Footnotes and cautions in the guideline have also been added and amended to link to the MHRA's latest advice and resources.*
April 2018:	CG127 – Update on website	*Footnotes and cautions in the guideline have been added and amended to link to the MHRA's latest advice and resources on sodium valproate. Medicines containing valproate taken in pregnancy can cause malformations in 11% of babies and developmental disorders in 30–40% of children after birth. Valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless alternative treatments are not suitable and unless the terms of the pregnancy prevention programme (http://www.ema.europa.eu/ema/index.jsp?*

		curl=pages/news_and_events/news/2018/03/news_detail_002929.jsp&mid=WC0b01ac058004d are met. This programme includes: assessment of patients for the potential of becoming pregnant; pregnancy tests; counselling patients about the risks of valproate treatment; explaining the need for effective contraception throughout treatment; regular (at least annual) reviews of treatment by a specialist, and completion of a risk acknowledgement form. In pregnancy, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation. See the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy (https://www.gov.uk/guidance/valproate-use-by-women-and-girls). *Appendices A and B (details of internal/external staff and committee members) were removed as this information is now available elsewhere on the NICE website.*
April 2018	CG127 – Updates from April 2018	*P12: Boxed update* *April 2018: The Medicines and Healthcare products Regulatory Agency (MHRA) has issued strengthened guidance on valproate. They state that valproate must not be used in pregnancy, and only used in girls and women when there is no alternative and a pregnancy prevention plan is in place. This is because of the risk of malformations and developmental abnormalities in the baby. See update information for details.* **1.9 Pharmacological treatment** **Sodium valproate** MHRA advice on valproate: In April 2018, we added warnings that valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless alternative treatments are not suitable and unless the conditions of the pregnancy prevention programme are met. Valproate must not be used in pregnant women. See also the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy. See update information for more details. Recommendations in this section offer alternative prescribing options for this group. Recommendations 1.9.1.10, 1.9.17.3, 1.9.17.6, 1.9.17.9 and 1.15.1.4 also provide additional specific information of relevance when considering prescribing AEDs to women of childbearing age.

		1.9.1.10 When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. Follow the MHRA safety advice on sodium valproate. [2018] **Research recommendations** - Comparison of efficacy of newer AEDs and standard AEDs - Initial and add-on treatment in childhood-onset epilepsy syndromes - Treatment outcomes in infantile spasms - Safety and efficacy of treatment for convulsive status epilepticus - **3.5 AEDs and pregnancy:** What is the malformation rate and longer term neurodevelopmental outcome of children born to mothers who have taken AEDs during pregnancy?

9 Warnings from other sources

Drug Therapeutics Bulletin

44. The Drug and Therapeutics Bulletin (DTB) provides summaries of the available evidence to support healthcare professionals in decision making. A full list of the relevant articles is included below.

Table F.8 *Articles in the Drug and Therapeutics Bulletin*

Issue	Title	Summary
April 1975 (Vol 13, No 9)	Anticonvulsants in pregnancy	• Most women have no change in the pattern of seizures, no changes to regular anticonvulsant therapy is required (aside from delay of administration in cases of morning sickness) • Folate supplementation to prevent anaemia • Congenital anomalies of the infant occur 2-3 times greater in babies born to mothers with epilepsy (cleft lip/palate, malformations of heart, CNS and GI tract, minor skeletal anomalies). • Reason for anomalies does not appear to be related to seizures or social factors associated with epilepsy. There does not appear to be a higher malformation rate in the children of women not receiving anticonvulsants but their epilepsy is likely to be much less severe. Genetic factors should be explored further. • "Present evidence suggests a teratogenic effect of anticonvulsant drugs." All commonly used anticonvulsants may bear some risk, but particular focus on phenytoin or a combination of phenytoin and phenobarbitone.

		• Risk to fetus not sufficient to justify stopping anticonvulsants, but may consider reducing dose in first three months. Additionally, in women planning to become pregnant and no longer experiencing seizures may consider reducing or withdrawing anticonvulsants prior to pregnancy, with support of specialist. • Perinatal mortality rate is doubled in babies of mothers taking anticonvulsants, due to congenital abnormalities and increased incidence of spontaneous haemorrhage. May consider giving Vitamin K to mother and baby.
December 1975 (Vol 13, No 25)	Sodium valproate and clonazepam for epilepsy	Overview of the two recently introduced antiepileptic drugs, including the evidence for efficacy. Lists unwanted effects of sodium valproate as: anorexia, nausea, drowsiness if taken with phenobarbitone or primidone, transient hair loss. Notes that there is evidence of teratogenicity in animals, but unknown risk in pregnant women (and if different from other antiepileptic drugs). Also notes unknown if there is a risk of malformation in offspring of men taking the drug. Advises that neither drug is recommended as drug of first choice until they have been more fully evaluated.
November 1976 (Vol 14, No 24)	New additions in the BNF 1976–78	"Sodium Valproate Tablets (Epilim) - An alternative to ethosuximide in the treatment of petit mal. Also useful in major epilepsy resistant to other drugs. Can be given with other drugs (DTB 1975,13,97). May be more teratogenic than other anticonvulsants."
September 1978 (Vol 16, No 20)	Drug causes of hair loss	Lists sodium valproate as a one medication which has been associated with hair loss.
November 1981 (Vol 19, No 24)	Sodium valproate reassessed	Overview of known pharmacology, pharmacokinetics, interactions and posology of sodium valproate. Describes recent reports of severe liver damage and other serious unwanted effects as "disturbing", and in contrast with early literature which "noted an almost complete lack of harmful effects from the drug." Reports on 30 known pregnancies in women taking valproate as monotherapy, of which 24 resulted in a healthy live birth, 3 children which were described as 'abnormal' and three spontaneous abortions. In cases with congenital abnormalities in the fetus, it considers the causal relationship to valproate to be uncertain.

		However, it concludes that "valproate is an effective drug and its potential dangers should not prevent its use in patients whose epilepsy cannot otherwise be controlled."
April 1989 (Vol 27, No 8)	Withdrawing antiepileptic drugs	Guidance on withdrawal of antiepileptic drugs and factors to consider. Does not mention pregnancy.
July 1990 (Vol 28, No 15)	Sodium valproate and spina bifida	Key information included: • Congenital abnormalities occur 2-3 times more often in babies born to mothers with epilepsy who are taking anticonvulsants • Women who take sodium valproate during the first trimester of pregnancy have a 1-2% risk of having a baby with spina bifida compared to 0.023% off all births in the UK. • There is no clear evidence linking sodium valproate with anancephaly or other major congenital abnormalities • Screening should take place in specialist centre with high resolution ultrasound and experienced technician. If maternal serum alpha fetoprotein is raised, amniocentesis should be performed to enable women to consider a termination. • No antiepileptic drug is free from teratogenic effects (suggests carbamazepine as 'probably the safest alternative') • Appropriate counselling should be offered to women and girls of childbearing age to enable them to choose for themselves.
September 1992 (Vol 30, No 19)	Lamotrigine – an add-on antiepileptic	Introduction of lamotrigine as 'add-on' treatment. Unwanted effects does not mention any teratogenic risks, and there is no warning about use in pregnancy.
April 1994 (Vol 32, No 4)	Gabapentin - a new antiepileptic drug	Introduction of a gabapentin as a 'add-on' treatment. Lists under precautions: "*Gabapentin is not teratogenic in animals, but its effects on the human fetus have not been evaluated. Whether gabapentin is excreted in milk is not known, but as a precaution lactating mothers should stop breastfeeding before starting gabapentin.*"
July 1994 (Vol 32, No 7)	Epilepsy and Pregnancy	Discussion of use of antiepileptic drugs in women who are pregnant or planning pregnant. Key information includes: • Women with untreated epilepsy, risk of giving birth to child with a malformation is about 25% higher than for the general population

		• Women taking antiepileptic drugs, risk is at least doubled • Most commonly minor (i.e. do not threaten health), major malformations (medical, surgical or cosmetic importance) are less common • Risk with all main AEDs (carbamazepine, phenobarbitone, phenytoin, sodium valproate), each has its own profile of risk (e.g. sodium valproate and spina bifida, hypospadias, craniofacial and skeletal) • Risk increased with number and dosage of AEDs • Pre-conception counselling should include information about risk, and advice from a specialist • There may be little or no benefit of switching drugs once a woman is already pregnant • Those taking sodium valproate and carbamazepine should be counselled and offered antenatal screening for spina bifida • Like all women, folic acid supplementation should take place before and for 12 weeks after, conception • 2/3 women do not experience change in seizure control • The fetus appears relatively resistant to effects of maternal seizures, although there is risk of trauma from falls, and intrauterine deaths have been reported • Maternal complications increased in women with epilepsy • "No one antiepileptic drug appears any less likely to cause fetal abnormality than any other." • Monotherapy is recommended, and dosage titrated against symptoms • "Epileptic women of childbearing age not wishing to become pregnant and taking an oral contraceptive should be treated with sodium valproate, which does not affect oral contraceptive efficacy, or given a higher dose of oral contraception." • The newer 'add-on' AEDs (gabapentin, lamotrigine, and vigabatrin) are not licenced for use in pregnancy
June 1998 (Vol 36, No 6)	Managing migraine	As part of guidance, sets out evidence for efficacy of sodium valproate in migraine prevention. Includes the warning: "*Women of child-bearing potential should be using adequate contraception, and be warned about the risk of teratogenicity, before sodium valproate is tried*."
Jun 2000 (Vol 38, No 6)	Tiagabine: add-on treatment for partial seizures	Introduction of tiagabine as add-on treatment. Includes the following precaution: "*Tiagabine is not recommended by the manufacturer for women who are, or are likely to become, pregnant or in those women who are breast-feeding."*

Dec 2000 (Vol 38, No 12)	Drug treatment of neuropathic pain	As part of guidance, discusses the evidence for efficacy and safety of the use anti-epileptics to treat neuropathic pain. Includes the following: "*In pregnancy, carbamazepine, phenytoin and sodium valproate all increase the risk of neural tube and other defects; use of anti-epileptic drugs for neuropathic pain is best avoided during pregnancy wherever possible.*"
Feb 2001 (Vol 39, No 2)	Managing childhood epilepsy	Review of diagnosis, investigation and treatment of children with common forms of epilepsy. Includes the following advice for use of AEDs to treat adolescent girls: "*Use of anti-epileptic drugs during pregnancy is associated with increased risk of teratogenicity, spina bifida and other birth defects. It is essential to discuss these risks, and the added importance, therefore, of effective contraception (and perhaps folate supplements) in any adolescent girl receiving anti-epileptic drug treatment.*"
June 2002 (Vol 40, No 6)	Oxcarbazepine for epilepsy - a useful new choice?	Introduces oxcarbazepine as add-on and monotherapy treatment for epilepsy. Includes the following: "*Oxcarbazepine should not be taken by women who are, or plan to become, pregnant, or who are breast-feeding.*"
June 2003 (Vol 41, No 6)	When and how to stop antiepileptic drugs in adults	In the UK, the drugs most commonly used first-line to suppress seizures are carbamazepine and sodium valproate Review of reasons and process for withdrawing antiepileptic drug treatment. Under 'Unwanted effects of drugs': "*There is an increased risk of fetal malformation in children born to women taking antiepileptic drugs, from 3% in the general population to 7% with one drug and 15% with two or more drugs.*" Includes following specific advice for women planning a baby: "*Women who wish to have a baby should be counselled about the risks from seizures in pregnancy compared with the risks of continuing medication. Where possible, any changes to medication should be completed prior to conception. If antiepileptic medication is to be continued during pregnancy, a single drug is preferable to combination therapy, and this*

		should be given at the lowest dose that controls seizures. Women with epilepsy who are planning a pregnancy should take folic acid 5mg daily in the pre-conception period and through at least the first trimester to reduce the risk of fetal malformation, whether or not antiepileptic medication is discontinued."
February 2005 (Vol 43, No 2)	Antiepileptics, pregnancy and the child	[Links to BNF Section 4.8 Antiepileptic Drugs] Review of evidence regarding pregnancy in women with epilepsy, and updates to advice on use of antiepileptic drugs. Opening paragraph states that potential contributory factors to the lower rate of healthy pregnancy outcomes in women with epilepsy include: antiepileptic drug therapy; genetic factors; socio-economic factors; seizures; or a lack of prenatal care. One possible explanation is that some AEDs impair the absorption and metabolism of folate, a key substance in fetal development. It emphasises that avoiding treatment also carries risks, e.g. people with epilepsy are 2-3 times more likely to die prematurely than those without epilepsy. "*So, the need to control epilepsy needs to be weighed against any risks of continuing antiepileptic medication in pregnancy.*" The review considers the limitations of the evidence available, and the complexity of comparing drugs and risk factors. It lists the following: • Stillbirths and neonatal loss are up to twice as likely among pregnant women with epilepsy (whether or not they take antiepileptic drugs) • Major congenital malformations occur in 2.4-4.5% of the general population, 0-8% of children of mothers not treated with antiepileptic drugs during pregnancy. They are 2-3 times more likely in children of mothers treated with antiepileptic drugs in pregnancy compared to the general population. The risk is increased with: first-trimester exposure, polytherapy, and appears higher in polytherapy that includes sodium valproate. • Minor malformations reported in up to 28% of infants exposed to antiepileptic drugs in utero, compared to 16% in general population. However also occur in children of mothers with untreated epilepsy. Notes that while in some cases become less apparent as child grows, multiple anomalies may be markers of more severe problems such as developmental delay. • Other warnings: intrauterine growth retardation; vitamin K deficiency and bleeding; drug withdrawal; sedation may occur in newborn if breastfeeding

		Discusses risks of specific drugs: • Carbamazepine – higher frequency of major malformations (heart defects, neural tube defects, hypospadias) than the general population or children of women treated with phenytoin • Sodium valproate – higher rates of malformations (neural tube defects, skeletal defects, hypospadias, heart defects), particularly at higher doses. Higher risk than alternative drugs (phenytoin, carbamazepine) • Phenytoin – 0.7 – 9.1%, similar to general population • Phenobarbital – rate of 2.4-6.5%, similar to general population or other AEDs • Primidone – 5.7-14.3% • Insufficient data regarding newer drugs, but based on animal studies and lack of evidence in humans, drug companies advise against use of topiramate, levitracetam, and pregabalin in pregnancy. Neurodevelopmental delay has been reported, although few studies have followed children up to pre-school or school age. Impaired neurodevelopment has been reported in studies of children exposed to sodium valproate (lower verbal IQ, additional educational needs), carbamazepine, phenytoin, and polytherapy. Action recommended: • Individualised preconception counselling to all women of childbearing age (including girls from the age of puberty, who may be attending paediatric units). Women should be advised to plan their pregnancy. Decisions should be made on withdrawal of medication, or lowest effective dose of monotherapy prior to conception. • Accumulating evidence that sodium valproate carriers great risk during pregnancy. Decisions should be carefully balanced in women with generalised epilepsy, where sodium valproate is often more effective than other drugs. It should not be started in women of childbearing age without advice from an epilepsy specialist. Notes that in practice, some switch to newer antiepileptic drugs, however they long-term effects are not known, and companies currently advise against their use in pregnancy. • Folic acid supplementation

		• If women present after conception, AED treatment should not stop abruptly. If within first trimester, should be started on folic acid. • Should be referred for obstetric care which includes detailed high-resolution ultrasound scanning
May 2005 (Vol 43, No 5)	Drug treatments for bipolar disorder: 2 Maintenance, prevention and special situations	Discusses the role of drug therapy for maintenance and prevention in patients with bipolar disorder, including special situations. Under 'Pregnancy and Lactation' it notes the increased risk of relapse to mania in the post-natal period. It warns that several of medications used in the treatment of bipolar disorder are associated with increased risk of teratogenicity, including lithium, valproate and carbamazepine. Advises that women should received appropriate advice about contraception, the benefits and the risks of treatment options if she wishes to become pregnant. This may include withdrawal of some or all medication, switching to less teratogenic drugs, or continuing with existing treatment. Women should also be given advice on antenatal diagnosis.
November 2011 (Vol 49, No 11)	Antiepileptic medication and breastfeeding	Update on new advice in the BNF on the use of antiepileptic medication in breastfeeding women.
June 2012 (Vol 50, No 6)	Updated SIGN guideline on perinatal mood disorders	Information on updated guideline from SIGN, which includes guidance that "*valproate (as a mood stabiliser) should not be routinely used in women of childbearing potential, because of the risk of teratogenicity and neurobehavioural toxicity.*"
February 2013 (Vol 51, No 2)	Perampanel: a new add-on treatment for epilepsy	Introduction of perampanel as new add-on treatment for epilepsy. Advises that it is not recommended for use in pregnancy. There is limited information from the use in pregnancy women. Animal studies showed embryotoxicity in rats at maternally toxic doses, although no indication of teratogenic effects in rats and rabbits.
June 2013 (Vol 51, No 6)	Prescribing in pregnancy—therapeutic discrimination?	A short overview of the ethical and medical challenges around prescribing in pregnancy. The authors state: "*The relative lack of information on the use of medicines during pregnancy remains an area of concern for healthcare professionals*." It describes the ethical issues around the exclusion of pregnant women from studies, even in drugs that are frequently used by pregnant women. Not knowing the risks can make it difficult for prescribers and patients to weigh these against the benefits. In the face of this lack of evidence,

		many patients are wary of taking medicines during pregnancy. The article points to sodium valproate as an example of a delay in adverse effects becoming apparent – "*sodium valproate was hailed as a wonder anticonvulsant in the 1960s, linked with neural tube defects in the 1980s and associated with adverse neurodevelopmental effects in the offspring with third trimester exposure in the 2000s."*
February 2014 (Vol 52, No 2)	MHRA warning on sodium valproate	Draws attention to MHRA special reminder to prescribers about evidence of long-term neurodevelopmental delays in children who are born to mothers prescribed sodium valproate in pregnancy.[102] Gives an overview of the risks and actions described by the MHRA. Comments that "*The latest advice from the MHRA is a reminder to prescribers to avoid use of sodium valproate in women of child-bearing potential, whenever possible. Until further guidance is reported from the EMA's ongoing review, prescribers are urged to follow the advice offered by the MHRA.*"
April 2015 (Vol 53, No 4)	Warnings and advice on valproate treatment	Draws attention to MHRA update[103] and EMA warnings[104] on the use of valproate medicines in women and girls. Gives an overview of the risks and actions described by the MHRA, information on where the information booklets can be found and includes the advice that valproate is now a black triangle medicine and is subject to additional monitoring. Comments that "*Healthcare professionals should ensure that they are familiar with the advice associated with the use of valproate in female children, adolescents, women of childbearing potential and pregnant women.*"
July 2017 (Vol 55, No 7)	Repeat warning on valproate in pregnancy as	Draws attention to MHRA alert on the risks of developmental disorders and birth defects associated with the use of valproate-containing medicines during pregnancy,[105] and evidence that despite previous communications to prescribers in January 2015[106] and February 2016[107], 1 in 5 women taking valproate are still not aware of the risk. Gives overview of the alert and advice for healthcare professionals. Comments: "*It*

[102]Sodium valproate: Risk of neurodevelopmental delay in children following maternal use. Drug Safety Update Vol 7, Issue 4. November 2013. See Table F.5.
[103] Medicines related to valproate: risk of abnormal pregnancy outcomes. Drug Safety Update Vol 8 Issue 6. January 2015. See Table F.5.
[104] EMA statement. CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls. 21 November 2014. Link here.
[105] Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures. Drug Safety Update Vol 10, Issue 9. April 2017. See Table F.5.
[106] Medicines related to valproate: risk of abnormal pregnancy outcomes. Drug Safety Update Vol 8, Issue 6. January 2015. See Table F.5.
[107] Valproate and risk of abnormal pregnancy outcomes: new communication materials. Drug Safety Update. Vol 9, Issue 6. February 2016. See Table F.5.

	message fails to raise awareness	*is of concern that such a simple message around such a major risk is proving difficult to implement. This highlights the need for all prescribers to systematically review their records to identify all girls and women of child-bearing potential who are currently taking valproate and related medicines. Given the limited success of previous initiatives, a new approach may be required to highlight and manage the risks associated with valproate products.*"
Oct 2017 (Vol 55, No 10)	Flagging risk	Acknowledges the challenge facing prescribers when balancing benefits and harms of a drug treatment. Concern that the process of communicating emerging issues on adverse effects is fragmented and not embedded into clinical practice. Discusses risk minimisation methods, and states that "*practical implementation of risk minimisation measures remains challenging. For example, many attempts have been made to highlight the risk of harm associated with the use of valproate medicines during pregnancy. Despite dissemination of safety alerts, communication material and educational resources, a significant number of women taking valproate remain unaware of any of the risks."*
April 2018 (Vol 56, No 4)	More recommendations to minimise exposure to valproate in pregnancy	Draws attention to the recommendations of the PRAC to prevent in utero exposure to valproate, following concerns that the previous initiative was not sufficiently effective.[108] Gives an overview of the key recommendations made by the PRAC. Comments: "*In the UK, the MHRA has issued a series of warnings related to the use of valproate medicines in pregnancy and the high risk of serious developmental disorders and congenital malformations. These latest recommendations from PRAC and the new valproate pregnancy prevention programme not only reflect the seriousness of these risks but also highlight the limited success of previous initiatives. An implementation strategy will be required to make sure that all healthcare professionals who prescribe, dispense or administer valproate are aware of their responsibilities.*"
Aug 2018 (Vol 56, No 8)	Valproate medicines - Pregnancy Prevention	Draws attention the Pregnancy Prevention Programme materials published by the MHRA,[109] and gives an overview of the key features. Comments: "*All healthcare professionals involved with prescribing, dispensing or monitoring the use of valproate products in women and girls of childbearing potential should ensure that they are familiar with the restrictions of the Pregnancy Prevention Programme and are using the support*

[108] EMA statement. PRAC recommends new measures to avoid valproate exposure in pregnancy. 9th February 2019. Link here.
[109] Valproate medicines (Epilim▼, Depakote▼): Pregnancy Prevention Programme materials online. Drug Safety Update Vol 11, Issue 10. May 2018. See Table F.5.

	Programme materials available	*materials with patients. Primary care prescribers should check that the Pregnancy Prevention Programme is in place for all women and girls of childbearing potential who are being prescribed valproate products*."

Manufacturer warnings

Changes to the warnings related to valproate use in pregnancy

45. Key information changes in the Datasheet/Summary of Product Characteristics (SmPC) and the Patient Information Leaflets (PIL) can be found in Section 4.

Direct warnings

46. Information was also communicated directly to doctors by the manufacturer (see table below for examples).

Table F.9 *Direct communication from the manufacturer to healthcare professionals*

Date	Type of warning	Details
1989[110]	Updated datasheet	Copies of the updated datasheet sent to GPs.
March 2016[111]	Letters sent to healthcare professionals in February 2016	Notification of letter sent to healthcare professionals in February 2016, regarding new communication materials about medicines containing valproate and the risk of abnormal pregnancy outcomes.
August 2017[112]	Letters sent to healthcare professionals in July 2017	Notification of letters sent to healthcare professionals, to supplement the previous communications and patient safety alert. These set out the actions required by specialists, specialist nurses/midwives, and general practitioners, and for pharmacists, referring to material provided previously.
August 2018[113]	Letters and drug alerts sent to healthcare professionals in July 2018	Dear Healthcare Professional letters were sent by Sanofi to doctors and pharmacists, informing them of "new contraindications, strengthened warnings and measure to prevent valproate exposure during pregnancy." This set out the key information and expected actions related to the pregnancy prevention programme.

[110] Sanofi written evidence to the Review
[111] Letters sent to healthcare professionals in February 2016. Drug Safety Update. Vol 8, Issue 8. March 2016
[112] Letters sent to healthcare professionals in July 2017. Drug Safety Update. Vol 11, Issue 4. August 2017
[113] Letters and drug alerts sent to healthcare professionals in July 2018. Drug Safety Update. Vol 12, Issue 1. August 2018

Professional Bodies and Regulators

47. The table below is based on information received from the professional bodies as part of the Review's Call for Evidence Process.

Table F.10 *Examples of warnings published by professional bodies*

Date	Professional body	Action
2015	RCPCH	Published leaflet for parents and carers, containing advice on sodium valproate and pregnancy in adolescent girls.[114]
2016	ABN	February 2016 – Statement on Sodium Valproate taken in Pregnancy[115]
2017	ABN	September newsletter: **"Use of Sodium Valproate in Epilepsy**: Following recent discussions about the risks associated with the use of sodium valproate in pregnancy, we have been asked by the MHRA to remind neurologists that sodium valproate has a license for epilepsy and bipolar disorder only, and we should prescribe it for other reasons (migraine, pain, sensory symptoms) to young women only with great caution, and possibly using a formal pregnancy prevention programme."
2017	ABN	**December newsletter:** **MHRA's Drug Safety Update team - advice for neurologists.** The December issue of Drug Safety Update is online now (link contained: Valproate medicines (Epilim▼, Depakote▼): Pregnancy Prevention Programme materials online)
2018	ABN	Spring newsletter: "**Valproate:** We have known for some time that children born to women who take valproate during pregnancy are at significant risk of birth defects and persistent developmental disorders with a 10% risk of birth defects, an average reduction in IQ estimated at 6-11 points and up to 30-40% risk of developmental disability. The MHRA have just published changes in the licence for Valproate following on from new measures from the European Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh). Simply put, the use of valproate in women of child-bearing age will not be allowed unless a pregnancy

[114] RCPCH, WellChild and NPPG. Sodium valproate for preventing seizures. March 2015 Available here.
[115] ABN General statement and statement.

		prevention programme is in place. The ABN epilepsy advisory group, together with input from the ABN council, have looked at this in detail and written the attached editorial published this month in Practical Neurology to help neurologists understand the new rules. We have also updated the advice on the ABN website. We strongly urge all neurologists to familiarise themselves with the new measures and the MHRA will discuss this during a dedicated session in the upcoming Birmingham ABN."
2018	ABN	**Late June newsletter:** During this year's ABN in Birmingham, the MHRA presented the new regulations which require women of childbearing potential taking valproate to be in a pregnancy prevention programme. There has been much debate about these new regulations before, during and since the meeting but we need to all be aware that these regulations are now in place and need to be adhered to regardless of individual opinions. As neurologists we know that valproate is a serious teratogen but we appreciate that it is also an effective anti-epileptic drug, and for some women with epilepsy, valproate may be the only drug that controls seizures. Until there is an equally effective safer alternative for this group of women we need valproate to remain available. To continue to have valproate available in the future, it is essential we observe the new regulations now. Discussions about its use must be informed. MHRA and ABN have provided information and resources already (links to MHRA, and ABN statements plus a Practical Neurology editorial[1] by Sanjay Sisodiya and the Epilepsy Advisory Group) but we realise that further guidance to deal with this issue for individual patients is needed and the ABN through the epilepsy advisory group will be producing further interpretative guidance over the coming months. The ABN recognises the need for a safe alternative to valproate to be developed and the need to lobby for research to be funded to enable this.
December 2018	RCPsych	Published position statement: Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness
2019	GPhC	July – Released video 'Supplying sodium valproate safely to women and girls'

10 Parliamentary reviews on epilepsy

Table F.11 *Parliamentary review on epilepsy*

"Cohen Report"[116] 1956	Recommended: • Provision of diagnostic and treatment clinics, longer-stay treatment and rehabilitation centres, led by a neurological physician with a team of paediatricians, psychiatrists, child guidance experts, radiologists, almoners, psychologists and others. • Investigatory centres for those with epilepsy and behavioural disorders, including an active out-patient clinic and follow-up system • Resettlement clinics working with general practitioner, almoner, disablement resettlement officer, local health and welfare authority services, and other relevant agencies. • Children should attend mainstream schools, and should not be sent to a special school until they have attended an assessment centre at a hospital. • Long-stay hospital units should be put into play for children with bad behaviour disorders • Epilepsy colonies should form part of the National Health Service, and be part of a unified national plan for the management of those with epilepsy. The aim should be to provide support to allow those with epilepsy to live an 'ordinary life' outside of the colonies in the future.
"The Reid Report"[117] 1969	Made 56 recommendations in total. These are summarised here:

[116] Medical care of epileptics: Report of the sub-committee of the Central Health Services Council. London: HMSO, 1956

[117] People with Epilepsy. Report of a Joint Sub-Committee of the Standing Medical Advisory Committee and the Advisory Committee on the Health and Welfare of Handicapped Persons. 1969. Available at the National archives LAB 19/883

	• "There should be greater awareness that the possibilities for prevention, treatment and care in epilepsy have extended in recent years" • *Diagnosis and continuing care* – sets out roles and expectations including: assessment by a multi-disciplinary team; regular review of dosage and suitability of long-term prescriptions; social worker support where required; expansion of neurological and neurosurgical facilities to provide adequate care • *Public attitudes* – including education of health care staff and the public • *Epileptic colonies* – sets out recommendations for admission and nature of services, and that colonies should expect to reduce their facilities as medical and social services expand • *Special centres* – for those with additional or complex needs should be established, which should have responsibility for research and teaching about epilepsy • *Needs at different ages* – considers the specific needs in childhood, the elderly, 'housewives' and 'unmarried mothers' • *Employment* - recommendations to enable those with epilepsy to enter or rejoin the workplace, including encouraging public and voluntary bodies to "set an example". • *Accommodation and voluntary agencies* – ensuring people with epilepsy are not discriminated against, and are supported if necessary, to find suitable accommodation • *Staffing of services* – appropriate training for those who work with people with epilepsy, including for nurses and social workers • There were also recommendations to assess the outcomes of these recommendations when they were put into action, and to reassess services for people in epilepsy in 5 years' time to ensure satisfactory development
Bennet investigation into the Reid Report[118] (unpublished)	
Report of the working group on services for people with epilepsy[119] (1986)	

[118] Bennet investigation into the Reid Report (J D Morgan and A E Bennet, unpublished reports)
[119] Report of the working group on services for people with epilepsy[119] 1986 Department of Health and Social Security

11 Hansard references to epilepsy or sodium valproate

Table F.11 *Hansard references to epilepsy or sodium valproate*

Date	Written/Debate	Title	Topics
17/11/1958	Written	Mental Health	Projects sponsored by the Medical Research Council in the sphere of mental health.
16/12/1958	Written	Epilepsy	Number of people working research project on epilepsy sponsored by the Medical Research Council.
28/02/1961	Written	Epileptics	Update on the recommendations of the Cohen Committee
29/03/1965	Oral Question	Epileptics (Report)	Update on the recommendations of the Cohen Committee
06/04/1965	Debate	Report On Care Of Epileptics	Requesting update on recommendations of the Cohen Committee, and discussion about provision of epilepsy services
21/04/1969	Written	Epilepsy	Available places for treatment of epilepsy; update on recommendations of the Standing Medical Advisory Committee on Epilepsy
12/01/1971	Written	Epilepsy	Research into causes and treatment of epilepsy
02/05/1971	Written	Epilepsy	Research into causes and treatment of epilepsy
27/01/1972	Debate	Care Of Epileptics: The Reid Report	Update on the recommendations of the Reid Report
21/02/1972	Motion	Chronically Sick And Disabled Persons	
29/06/1972	Written	Epileptics (Special Centres)	Financing of special centres for epilepsy in Scotland
15/07/1973	Written	Epilepsy	Financing of special centres for epilepsy in Scotland
03/05/1976	Written	Epileptics	Support of those with epilepsy
24/03/1977	Written	Epilepsy	Closure of specialist hospitals for epilepsy

28/11/1977	Written	St Faith's Hospital, Brentwood	Closure of specialist hospital for epilepsy
29/11/1977	Written	Epilepsy	Closure of specialist hospitals for epilepsy
08/11/1978	Written	Espilepsy [sic]	Spending on treating epilepsy
08/12/1978	Written	Cystic Fibrosis	Ongoing research in the field of perinatal and infant mortality
22/05/1981	Written	Epilim	Safety of sodium valproate use in children; response states that a writ has been issued alleging negligence on the part of the manufacturers of Epilim.
06/07/1981	Bill Amendment (Lords)	Education Bill	Provision of special educational needs services; question is raised about children attending schools/homes run by voluntary associations
27/07/1981	Written	Sodium Valproate	Adverse effects of sodium valproate
28/07/1981	Written	Epilim	Safety of sodium valproate
31/07/1981	Written	Sodium Valproate	Adverse effects of sodium valproate
27/04/1982	Written	Epilim	Adverse effects of sodium valproate
03/02/1983	Written	Epilim	Sodium valproate adverse events in pregnancy
09/03/1983	Written	Sodium valproate	Adverse effects of sodium valproate
15/03/1983	Written	Sodium Valproate	Adverse effects of sodium valproate reported to the CSM
23/03/1983	Written	Sodium Valproate	Adverse effects of sodium valproate reported to the CSM [reply to 15/03/1983]
18/04/1983	Written	Epilim	Safety of sodium valproate
28/04/1983	Written	Epilim	Safety of sodium valproate [reply to 18/04/1983]
21/01/1985	Written	Epilim	Adverse effects of sodium valproate - datasheet
29/01/1985	Written	Epilim	Adverse effects of sodium valproate - datasheet [reply to 21/01/1985]
29/01/1986	Written	Epilepsy	Epilepsy service provision in Scotland
23/05/1991	Written	University Hospital Of Wales	Epilepsy service provision in Wales
05/07/1991	Debate (Lords)	Epilepsy Research: Expenditure	Funding of epilepsy research by the MRC
09/03/1994	Written	Sodium Valproate	Sodium valproate adverse events in pregnancy

17/01/1995	Debate	Epilepsy	Funding of epilepsy research; employment of people with epilepsy by the NHS
18/04/1995	Written	Maudsley Hospital	Specialist hospital for epilepsy
24/04/1995	Written	Centre For Epilepsy	Specialist centre for epilepsy
10/07/1995	Written	Centre For Epilepsy	Specialist centre for epilepsy
12/07/1995	Debate	Cannabis (Therapeutic Use)	Specialist prescribing of cannabis; mentions sodium valproate unlicensed use for pain relief
17/07/1995	Written	Epilepsy Research	Research into treatment of epilepsy
24/10/1995	Written	Epilepsy	Centres of excellence; sodium valproate syndrome; informing healthcare professionals and the public about epilepsy
24/07/1996	Written	Epilepsy	Research into treatment of epilepsy
01/04/1997	Debate	National Health Service	Wider debate on the NHS; draws attention to the number of reports regarding provision of epilepsy services
17/06/1998	Debate	Epilepsy	Focus on: care for those who are living with epilepsy; improving the treatment available and raising public awareness about epilepsy; research into sudden death in epilepsy.
02/12/1998	Written	Anti-Convulsant Drugs	Safety of anticonvulsants in pregnancy
15/12/1998	Written	Sodium Valproate	Sodium valproate adverse events in pregnancy
09/03/1999	Debate	Meath Home	Role of voluntary organisations; funding of long-term care
26/04/1999	Written	Lamotrigine	Inquiries received about lamotrigine by the MCA
25/05/1999	Written (Lords)	Anti-Epileptic Drugs In Pregnancy	Interactions between anticonvulsants and oral contraceptives; safety of anticonvulsants in pregnancy
28/02/2000	Debate (Lords)	Epilepsy	Service provision for people with epilepsy
10/03/2000	Written	Epilim	Sodium valproate use in children and pregnant women
24/05/2000	Written (Lords)	Epilim	Sodium valproate use in children
09/01/2001	Debate	Nhs (Somerset)	Service provision for people with epilepsy
09/04/2001	Written	Epilepsy	Hospital admissions

23/01/2002	Written	Child Illnesses	Children with chronic illness
23/05/2002	Debate	Epilepsy	Service provision for people with epilepsy
10/06/2002	Written	Epilepsy	Sudden unexpected death from epilepsy
19/09/2002	Written	Epilepsy	Epilepsy deaths; service provision for people with epilepsy
02/12/2002	Writttten	Belfast City Hospital	Specialist epilepsy nursing provision in Northern Ireland
22/01/2003	Debate	National Service Framework For Long-Term Conditions	National Service Framework; shortage of specialist service provision
06/03/2003	Debate (Lords)	Epilepsy	Service provision for people with epilepsy
08/04/2003	Debate	Specialised Health Services	Commissioning of specialised health services
18/11/2003	Written	Epilepsy	Specialist epilepsy nursing provision
09/12/2003	Oral Question	Epilepsy Nurses	Specialist epilepsy nursing provision
17/12/2003	Written	Epilepsy	National Service Framework; specialist service provision
10/02/2004	Debate	Health Funding (Buckinghamshire)	Health funding; effect of specialist service provision
15/03/2004	Written	Epilepsy	Cost of epilepsy medication to the NHS
25/01/2007	Debate	Health and Care in the Community	Health and social care
01/05/2007	Debate	Health: Specialist Nurses	Reduced spending on specialist nurses; including specialist epilepsy nursing
10/07/2007	Written	Social Security Benefits: Epilepsy	Number of people receiving disability benefit for epilepsy
17/07/2007	Debate	Epilepsy Services	APPG Wasted Money, Wasted Lives Report; special needs of WOCBAs with epilepsy; NICE guidelines not being followed.
27/11/2007	Written	Queen's Hospital Romford: Epilepsy	Specialist epilepsy nursing provision in Romford
03/06/2008	Written	Epilepsy: Research	Funding for epilepsy research
01/09/2008	Written	Epilepsy	Funding for epilepsy centres; training in epilepsy awareness
24/02/2009	Debate	Epilepsy	Guidelines not being followed; shortage of specialist epilepsy service provision
02/03/2009	Written	Social Security Benefits	Number of people receiving disability benefit for foetal valproate syndrome

03/03/2009	Written	Foetal Anti-convulsant Syndrome	Number of people diagnosed with foetal valproate syndrome
03/07/2009	Written	Disability Living Allowance: Epilepsy	Number of people receiving disability benefit for epilepsy
03/12/2009	Debate	Health: Epilepsy	Implementation of NICE guidance; specialist epilepsy nursing provision
26/02/2010	Written	Sodium Valproate	Sodium valproate adverse events in pregnancy
11/10/2010	Debate (Lords)	Health: Neurological Conditions	Allied health professionals in health and social care for people with long-term neurological conditions;
12/10/2010	Debate	Epilepsy Services	Service provision for people with epilepsy; data; key issues including advice to women of childbearing age
24/11/2010	Debate	Epilepsy and Related Conditions (Education and Health Services)	Provision of education, health and other support for people with epilepsy and related conditions
30/11/2010	Debate (Lords)	Provision of Epilepsy Services	Service provision for people with epilepsy; sodium valproate use in pregnancy; FACS litigation
29/11/2011	Debate	Epilepsy	Prevention of avoidable deaths from epilepsy; service provision for people with epilepsy; NICE guidelines not being followed
08/12/2011	Debate	Health: Neurological Conditions	Support for people with neurological conditions; specialist epilepsy service provision
20/11/2012	Debate	Health: Neurological Services	Improvements to neurological services, including epilepsy services
29/01/2013	Debate	Epilepsy	Impact of local and national health service changes on people with epilepsy; 'A Critical Time for Epilepsy in England' report
26/03/2013	Debate	Fetal Anti-convulsant Syndrome	Fetal anti-convulsant syndrome, focussing on sodium valproate
26/11/2013	Oral Question	Compassionate Care (NHS)	Lack of counselling about risks of sodium valproate during pregnancy

09/06/2014	Debate	Children with Epilepsy (Children and Families Act 2014)	Epilepsy and education
02/02/2015	Oral Question (Lords)	Epilepsy: New Treatments	Availability and accessibility of new epilepsy medications and treatments
26/02/2015	Debate	Epilepsy	Raising broad issues about epilepsy including: stigma; information about risks; sodium valproate; enforcement of guidance; SUDEP; and benefits.
24/06/2015	PMQs	PMQ Engagements	Sodium valproate adverse events in pregnancy (history)
19/10/2017	Debate	Valproate and Foetal Anticonvulsant Syndrome	Sodium valproate adverse events in pregnancy; history - awareness of risk and lack of communication to women
14/12/2017	Debate	Vulnerable Children	Care and social services for vulnerable children; healthcare plans at school for children with epilepsy
19/12/2017	Oral Questions	Topical Questions	Warnings about sodium valproate adverse events in pregnancy
21/02/2018	Debate	Medicines and Medical Devices Safety Review	Announcement of the IMMDS Review
22/02/2018	Debate (Lords)	Medicines and Medical Devices Safety Review	Announcement of the IMMDS Review
09/03/2018	Written	Pregnancy: Sodium Valproate	Cost of provision of special educational needs and disability support for children with foetal valproate syndrome
16/04/2018	Oral Questions	Cannabis Oil Prescription: Epilepsy	Licensing of cannabis oil for epilepsy treatment
24/04/2018	Written	Sodium Valproate Regulation	Outcome of EU review into the safety of sodium valproate
19/06/2018	Debate	Epilepsy Guidance (Autism)	Inclusion of autism in NICE guidance about epilepsy
10/07/2018	Written	Independent Medicines and Medical Devices Safety Review Update	Announcement of 'pause'

28/02/2019	Debate (Lords)	Safety of Medicines and Medical Devices	Raises number of issues regarding safety of medicines and medcial devices, and more broadly in healthcare sector; update on the Review
04/03/2019	Oral Question (Lords)	Cannabis: Medicinal Use	Licensing of cannabis for epilepsy treatment
21/03/2019	Debate	Valproate Pregnancy Prevention Programme	Implementation of Valproate Toolkit and the Pregnancy Prevention Programme