

# **The Independent Medicines and Medical Devices Safety Review**

## **Written Evidence**

### **Patient Groups: Sodium Valproate**

Published December 2018

Updated January 2019

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### Disclaimer

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**WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.**

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22 October 2018

Dear Baroness Cumberlege,

### Formal Response To The Cumberlege Review From The Epilepsy Society

Please find enclosed the formal written evidence submitted to your Review from the Epilepsy Society. We welcome this opportunity to respond to the Review and wish you and your colleagues every success with your important work.

In addition to the formal response, I would like to add some personal comments informed by my experience of engaging with a wide range of people as the Epilepsy Society has tried, with others, to raise awareness of the risks posed to an unborn baby if their mother were prescribed sodium valproate. This engagement includes membership of the MHRA Expert Working Group on Sodium Valproate, although I was asked to sign a confidentiality agreement in respect of that Group.

First, I would like to pay tribute to the victims whose babies were harmed by sodium valproate. They have campaigned for decades to raise awareness of the serious risks and we owe them a debt of gratitude. They have also over the years been supported by their families, charities, friends and many other supporters but their contribution has been unique: they have led from the front and provided outstanding service to others.

Second, I would like to pay tribute to the Government. It is no easy task for the then Secretary of State for Health & Social Care to respond to decades of inaction with such a positive intervention. And, moreover, to set up the Review to promote understanding and improvements to the culture and the system that led first to the original mis-judgements and, subsequently, to the absence of any proportionate or timely response.

Third, I would like to draw your attention to the question in particular of culture as a possible contributory factor. I think that it would be right for you to consider whether medically-qualified professionals gave sufficient weight to information provided to them in part because the source was non-medically qualified people, largely women patients, and/or because the issues largely concerned women's health. A relevant question would be whether, in your opinion, any of those cultural issues persist today; and, if so, what can be done to bring about a change for the better.

Fourth, and finally, I would be very interested in your conclusions from the evidence on how the regulatory system can be improved. I think that it would be helpful for there to be a particular focus on:

- the responsiveness of the MHRA to the concerns of patients and others;
- the ability of the MHRA to communicate effectively with healthcare professionals and to alter their practice; as well as their ability to communicate with patients; and
- the accountability of the MHRA to the Government and to Parliament; and the robustness of the systems that support that accountability.

I hope that these comments are a helpful contribution to your work. I would of course be pleased to discuss them with you, or to support the work of the Review in any other way that would be helpful.

Yours sincerely

Clare Pelham

Clare Pelham  
Chief Executive



### About the Epilepsy Society

1. **About the Epilepsy Society** – Our vision is a full life for everyone affected by epilepsy. We want everyone affected by epilepsy to have the best opportunity for a full life – as free from seizures as possible. We set out to make a difference to every person affected by epilepsy whatever their background, however seriously it affects them, and whether they have the condition themselves or are close to someone with epilepsy.
2. Our mission is to enhance the quality of life of people affected by epilepsy by promoting public awareness and education, by undertaking research and by delivering specialist medical care and support services.
3. **Our work at Epilepsy Society** - More than half a million people in the UK have epilepsy and one third have seizures that cannot be controlled through available anti-epileptic drugs. There are 1,000 deaths from the condition every year, including many children and young adults. Epilepsy can have a devastating effect on people and their families, affecting all aspects of their lives.
4. Epilepsy Society is the UK's leading provider of epilepsy services. Through our cutting edge research, awareness campaigns, information resources and expert care, we work for everyone affected by epilepsy in the UK.
5. Our research is driven by the desire to understand what has caused the epilepsy in each individual person, to be able to identify the best therapy from the outset, and to make this expertise widely available.
6. Epilepsy Society's Chalfont Centre is the UK's largest epilepsy specialist provider of care services. We provide a service and environment that supports all those with epilepsy to live a better and more fulfilling life.
7. We are part of a unique arrangement with University College London and the National Hospital for Neurology and Neurosurgery. This ensures academic and clinical excellence, patient input and relevance of our medical research. We are also a World Health Organisation (WHO) Centre of Excellence.
8. For more information visit: [www.epilepsysociety.org.uk](http://www.epilepsysociety.org.uk)

### Our response to the Review

9. The Epilepsy Society welcomes the opportunity to respond to this Review and welcomed the decision by the previous Secretary of State for Health and Social Care for it to take place.
10. The sad reality is that too many women of child-bearing age are still not aware of epilepsy medicine risk in pregnancy.

11. We have been campaigning on this issue over many years in partnership with Young Epilepsy and Epilepsy Action – in close collaboration with women affected by this issue and victims' groups – to ensure women of child-bearing age have the information they need to make informed choices about the risks of taking sodium valproate during pregnancy.
12. In September 2017 the Epilepsy Society – in partnership with Young Epilepsy and Epilepsy Action – published the findings of a survey (appendix A) we conducted as to the views of women with epilepsy taking sodium valproate. This followed a similar survey the previous year (appendix B).
13. The findings of the 2017 survey revealed that almost one-fifth (18%) women and girls of childbearing age currently taking the epilepsy medication, sodium valproate, do not know it can harm the development and physical health of their unborn child should they become pregnant.
14. The survey also revealed that more than a quarter (28%) of women and girls of childbearing age taking the epilepsy drug have not been given information about risks for their unborn child.
15. More than two thirds (68%) of women and girls of childbearing age taking the epilepsy drug had not received specially produced valproate materials released in February 2016.
16. Almost one-fifth (18%) women and girls of childbearing age currently taking the epilepsy medication sodium valproate do not know it can potentially harm the development and physical health of their unborn child should they become pregnant.
17. More than 2,000 women and girls of childbearing age with epilepsy took part in the survey which revealed that just over a quarter (28%) of women and girls of childbearing age who responded, and are currently taking sodium valproate, had not been given information about risks for children exposed to the drug during pregnancy.
18. It is estimated that around 10% of babies born to women who take sodium valproate during pregnancy are born with physical disabilities. Up to 40% are at risk of developmental issues that can lead to learning difficulties. They can affect a child's learning and understanding, behaviour and language and manifest in ways such as attention deficit hyperactivity disorder (ADHD) or autistic spectrum disorders.
19. In September 2016, Epilepsy Society presented the findings of the survey as part of our joint submission to the European Medicines Agency Public Hearing into sodium valproate (appendix C).
20. In the UK approximately 35,000 women take sodium valproate medication and it is the third most-prescribed anti-epilepsy medicine. The medication is also prescribed for people with bipolar disorder.

Monday 22 October 2018.

21. New MHRA Regulations in Place – While we welcome the new regulations that have been put in place by the MHRA to help reduce the number of pregnancies with avoidable birth abnormalities, we believe the Review has an important role to play in assessing how effectively they have been implemented and the scope for improvement in the dissemination of this information among health and pharmaceutical professionals.
22. In April 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) introduced new regulations around the way in which the anti-epileptic drug sodium valproate is prescribed to women and girls of childbearing age.
23. The most important change announced in the regulations was every woman and girl of childbearing age who has been prescribed sodium valproate is entitled to see her doctor every year to discuss the risks of this drug to an unborn baby. It is expected that every patient will leave the discussion with an important written reminder of the risks if sodium valproate is taken during pregnancy. This means that the patient should be able to make informed choices about whether to plan a pregnancy and her future medical treatment.
24. We call upon the Review to assess how effective the MHRA have been in disseminating its revised toolkit to health care professionals and the extent to which women of child-bearing age are receiving an annual health check with their GP on this matter; and what steps the MHRA and the NHS more widely are putting in place to disseminate best practice, monitor overall performance and support those areas which are not meeting the requirements set out in the regulations.
25. We also call upon the Review to recommend that the MHRA undertakes a high profile, public facing information awareness campaign – properly resourced and supported – to help in raising awareness of the risks to women of child-bearing age. We believe the MHRA should be made publicly accountable for these measures and be expected to present to Ministers and Parliament their audited achievements against their key deliverables in this area.
26. Reaching Out – One of the key issues raised by victims, and by victims’ organisations is the extent to which they feel their voices have been ignored and their views not taken seriously. This Review is a welcome – if long overdue – response to these concerns. Therefore it is particularly important for the Review to learn the lessons from these experiences and ensure the views of victims are the centre of the Review process and that their concerns are listened to with compassion and sensitively.
27. It is also important that the Review is pro-active in terms of the way in conducts itself as part of this review process and fully engages with those who may want to participate. In particular we would urge the Review to hold events and meetings across the country and to ensure these are properly publicised and promoted with a particular focus on hard-to-reach groups.

**Monday 22 October 2018.**

28. As part of the Review process the Epilepsy Society would also welcome the opportunity to provide oral evidence, building on our background and years of campaigning on this issue. We would also welcome the opportunity to discuss with the Review Team how we can help further utilise our own networks and reach across the country to promote the Review and play our role to ensure a high level of participation among victims' groups and their representatives.
  
29. The Epilepsy Society will also be conducting a repeat version of the survey with women of child-bearing age with our partner organisations in the future and would welcome the opportunity to present these interim findings to the Review, if the timings allow.
  
30. Evidence submitted by Clare Pelham, Chief Executive.  
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## Sodium Valproate Survey 2017 – Final Results



The “Sodium Valproate and pregnancy” survey developed by the UK’s three main epilepsy charities, with input from MHRA, ran between 17 August and 27 November 2017. The survey was for girls and women with epilepsy under the age of 50 in the UK and garnered 2,350 responses. The survey remains open .

A summary of the main results is below:

### 1. Awareness

Of the 2,350 respondents to the survey, only 661 (28%) are currently taking sodium valproate.

The survey showed that **20% (132) of women currently taking sodium valproate did not know that sodium valproate “can, in some cases, negatively affect the development and/or physical health of children born to women taking this medication”.**

The proportion of women unaware of the risks increases slightly when respondents who have taken sodium valproate in the past, but no longer take it, are included (26%).

**41% of all respondents (960) did not know of the risks.**

### 2. Discussions with healthcare professionals

**28% (185) of women currently taking sodium valproate have not had a discussion initiated by a HCP about pregnancy and sodium valproate.**

A neurologist was most likely to initiate this discussion (for 55% of respondents), followed by a GP (42%), Epilepsy specialist nurse (32%) and pharmacist (7%).

The proportion of women who have not had a HCP-initiated discussion about pregnancy and sodium valproate increases when those who have taken sodium valproate but are not currently on the medication, are taken into account (32% of all respondents to the question). In this group, a neurologist was most likely to initiate this discussion (for 52% of respondents), followed by a Epilepsy specialist nurse (30%), GP (33%), and pharmacist (5%).

### *In 2017*

The survey indicates that 13% of all respondents have not seen a neurologist, GP, epilepsy specialist nurse, pharmacist, or any combination of those HCPs in 2017 (this figure was 9% in 2016). For women currently taking sodium valproate, 14% have not seen a healthcare professional in 2017.

## Appendix A

Of the same group, 32% had their most recent discussion this year, 16% in 2016, 26% between 2000 and 2015 and 10% had their last discussion on the topic before the year 2000. 16% have never had a discussion with a HCP about sodium valproate.

Of the women currently taking sodium valproate, 33% have not been given information about risks for children born to women taking sodium valproate; more than half (51%) have not been given information about contraception; and 25% have not been given information about the importance of continuing with their AEDs.

### 3. Toolkit materials dissemination

**In 2017, 70% of women currently taking sodium valproate have received none of the valproate toolkit materials released in February 2016.**

Of this group, 18% have received a verbal checklist of the risks of using the drug during pregnancy from a HCP; 13% have received the booklet explaining the risks; and 6% have received the card from a pharmacist.

**In 2016, 68% of women currently taking sodium valproate received none of the valproate toolkit materials released in February 2016.**

20% have received a verbal checklist of the risks of using the drug during pregnancy from a HCP; 16% have received the booklet explaining the risks; and 6% have received the card from a pharmacist.

## Appendix A

Comparative results between 2017 and 2016 sodium valproate awareness surveys, carried out by Epilepsy Society, Epilepsy Action and Young Epilepsy.

See next page

## Appendix A

### Appendix A

Comparative results between 2017 and 2016 sodium valproate awareness surveys, carried out by Epilepsy Society, Epilepsy Action and Young Epilepsy.

Survey results for girls and women with epilepsy under the age of 50, in the UK.

**2017 survey** 17 August – 27 November 2017

2,350 responses (661 women and girls currently taking sodium valproate)

**2016 survey** 24 April – 04 June 2016

2,788 responses (515 women and girls currently taking sodium valproate)

( ) figures from 2017 survey

	<b>2017</b>	<b>2016</b> ( )
<b>Number of women taking SVA who have not had a discussion initiated by an HCP about pregnancy and SVA</b>	28%	27%
<b>Number of women on SVA who have not seen an HCP</b>	14%	(9% )
<b>Number of women taking SVA who have not received the valproate toolkit materials released in February 2016</b>	70%	80% (68%)
<b>Number of women on SVA who have not been given information about risks of drug during pregnancy</b>	33%	35%
<b>Number of women on SVA who have not been given information about contraception</b>	51%	49%
<b>Number of women taking SVA who have received a verbal checklist of risks around SVA during pregnancy</b>	18%	11% (20% )
<b>Number of women taking SVA who have received a booklet explaining the risks</b>	13%	10% (16%)
<b>Number of women on SVA who received a card from the pharmacist</b>	6%	6% (6%)



## Sodium Valproate Survey – Results summary



The “Sodium Valproate and pregnancy” survey developed by the UK’s three main epilepsy charities, with input from MHRA, ran for six weeks between 24 April and 4 June 2016. The survey was for women with epilepsy between the ages of 18 and 50 in the UK and garnered 2,788 responses.

A summary of the main results is below:

### 1. Awareness

Of the 2,788 respondents to the survey, only 624 (22%) are currently taking sodium valproate.

The survey showed that **20% of women currently taking sodium valproate did not know** that sodium valproate “can, in some cases, negatively affect the development and/or physical health of children born to women taking this medication”.

The proportion of women unaware of the risks increases slightly when respondents who have taken sodium valproate in the past, but no longer take it, are included (27%). Interestingly, a higher proportion of respondents (882 respondents: 32%) were former users of sodium valproate, than those who currently take the medication.

**Nearly half of all respondents (48%) did not know of the risks.**

### 2. Discussions with healthcare professionals

**27% of women currently taking sodium valproate have not had a discussion** initiated by a HCP about pregnancy and sodium valproate.

A neurologist was most likely to initiate this discussion (for 54% of respondents), followed by a GP (45%), Epilepsy specialist nurse (36%) and pharmacist (4%).

The proportion of women who have not had a HCP-initiated discussion about pregnancy and sodium valproate increases dramatically when those who are not currently on sodium valproate are taken into account (54% of all respondents to the question). The ranking of most likely HCPs to initiate the discussion remains the same however.

#### ***In 2016***

The survey indicates that around half of all respondents have seen a Neurologist, GP, Epilepsy specialist nurse, pharmacist, or any combination of those HCPs in 2016. This proportion is very similar for women currently taking sodium valproate, perhaps 3-4% higher.

The survey also indicates that discussions around the risks of taking sodium valproate are not significantly more likely to have taken place in 2016 than years past.

**Women taking sodium valproate who have seen a HCP in 2016 are between 1-2% more likely to have had a HCP initiate such a discussion (Annex A).**

Of the same group, 30% had their most recent discussion this year, 39% between 2000 and 2015 and 12% had their last discussion on the topic before the year 2000.

### 3. Toolkit materials dissemination

**80% of women currently taking sodium valproate have received none of the valproate toolkit materials released in February 2016.**

Obviously this number decreases for those who have seen a HCP this year, but only to 77% (Annex B). This also indicates some confusion or an inconsistency between answers, given the materials have only been available in 2016. It also shows the effect of respondents skipping certain questions.

Of the latter group, 12% have received a verbal checklist of the risks of using the drug during pregnancy from a HCP; 11% have received the booklet explaining the risks; and 6% have received the card from a pharmacist.

#### ***Dissemination rate by HCP***

Rates of receiving the toolkit materials in 2016 did not change much when adjusting the survey results for specific HCPs and the specific materials they've been asked to disseminate.

222 respondents mention having seen their GP this year. 11% of those received the booklet and the same proportion received the verbal checklist.

Of those who confirmed they've been to a pharmacist in 2016 (88 respondents) only 4 said they'd received the card (5%). Again this suggests confusion or shows the effect of a number of people skipping question 4, as an additional 28 people taking sodium valproate claimed to have received this card.

### 4. Outcomes of discussions

The chart below shows the outcomes of discussions with HCPs about sodium valproate and pregnancy, based on the year the *most recent* discussion was held.

Result	Year of last discussion			
	Overall	2016	2000-2015	Before 2000
Continued taking SV	29%	48%	28%	40%
Stopped taking SV	29%	16%	34%	42%
Prescribed SV for first time	6%	6%	8%	5%
Continued not taking SV	36%	30%	30%	14%

## Appendix B

The only consistent trends shown are that the number of people that have stopped taking sodium valproate as a result of their most recent discussion with a HCP on the issue is decreasing, while the number that continued to take a different AED is increasing.

These figures may not mean much in isolation. The reasons surrounding patients' drug choices (questions 11, 12 and 14) must be taken into account.

For instance, while a higher percentage of patients have decided to continue taking sodium valproate following discussions in 2016 than from 2000-2015 (48% v 28%), fewer have done so as a result of their doctors saying it is the right drug for them. Following discussions in 2016, 14% used this reason for staying on sodium valproate, while 24% used the same reason for most recent discussions from 2000-2015.

A higher proportion of those who have held discussions in 2016 on the issue with HCPs chose to stay on the drug because they are/were not planning a pregnancy: 57% v 40% from 2000-2015 (see Annex C and D).

### 5. Discussion topics covered

The survey asked about the specific aspects of counselling provided by HCPs in relation to sodium valproate and pregnancy (Annex E: note this only includes those who said they'd had a discussion with a HCP in question 3).

In discussions with HCPs on the issue, women with epilepsy on sodium valproate were most likely to be told about the risks for children born to women taking the drug (81%), followed by the importance of continuing to take AEDs to control their seizures (79%), followed by contraception (57%).

Unfortunately the survey doesn't reveal which healthcare professionals were more likely to address each specific issue. Future surveys should perhaps address this more directly.



**Joint oral submission by Epilepsy Society and Epilepsy Action to European Medicines Agency public hearing in sodium valproate 26 September 2017**

To be presented by Clare Pelham, chief executive, Epilepsy Society on behalf of both Epilepsy Society and Epilepsy Action

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**What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?**

There is no doubt that for some women with epilepsy, sodium valproate (SVA) is the only medication that will control their seizures. However the drug can pose a significant risk to an unborn child if taken during pregnancy, particularly when prescribed at higher doses. Up to 40 per cent of babies born to women prescribed SVA are at risk of developmental issues that can lead to learning difficulties and about 10 per cent are at risk of a physical disability such as spina bifida.

**What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?**

Both Epilepsy Society and Epilepsy Action have been actively campaigning on this issue for several years. Epilepsy Action campaigned for the introduction of the QOF indicator for preconception counselling, now retired. Alongside campaigning, Epilepsy Society has led on an international consortium to try to identify, through genetics, those women for whom sodium valproate would pose the greatest risk during pregnancy.

Most recently the two charities, together with Young Epilepsy, have worked alongside the Medicines and Healthcare products Regulation Agency (MHRA) and other interested bodies to ensure that women and healthcare professionals have the right information about sodium valproate and are aware of the risks associated with the drug. This has included advising on an MHRA toolkit, launched in February 2016..

Prominent warnings about risks during pregnancy have been added on the labelling of valproate- medicines and the MHRA sent a Patient Safety Alert through the NHS Central Alerting System. They also produced a letter for GPs to use to arrange reviews for all women and girls in their practice taking sodium valproate.

However, last year when we surveyed 2,700 women with epilepsy, 20 per cent of those who were taking sodium valproate were not aware of the harm it could cause to the development and physical health of an unborn child.

This year we have repeated the survey (2,000 women)and found that although this figure has improved slightly, 16 per cent (1 in 6) of women taking sodium valproate were still not aware of the risks. **All** women taking this drug should be aware - without exception.

21 per cent of respondents who were taking sodium valproate had not had a discussion led by their healthcare professional about risks around pregnancy and sodium valproate. 68 per cent of women on sodium valproate had still not received the MHRA toolkit released in February 2016. While the toolkit is a

useful resource, much more needs to be done – urgently - to make sure it's reaching the right people.

Although our survey showed that 86 per cent of women on sodium valproate had seen a healthcare professional in 2017, more than a quarter of them (27 per cent) had not been given information about risks..

Measures currently in place are arguably moving in the right direction, but the information is still clearly not reaching the right people. The statistics vary slightly from 2016 to 2017, but the clear and consistent picture is one where approximately 20 percent or 1 in 5 women with epilepsy who are taking sodium valproate are not aware of the risks or have not been given appropriate information.

The reasons are many fold:

- there is no NHS audit or register of women with epilepsy which could flag up the need to call them in for review.
- annual reviews for women with epilepsy are recommended in NICE guidelines but are not mandatory.
- information is available but conversations are not always happening.
- women with epilepsy often experience memory issues either as part of their condition or as a side effect of their medication. Warnings must be repeated on a regular basis and in written form as well as orally.

**What other measures should be taken to reduce the risks of using valproate during pregnancy?**

Epilepsy Society is calling on Jeremy Hunt to make the following change immediately:

**Repeat prescriptions for sodium valproate for women and girls of childbearing age should not be routinely renewed for more than 12 months without a face-to-face consultation with a doctor or nurse. This consultation must include personal and tailored information about the risks around sodium valproate during pregnancy. The information should also be provided in written format.**

This will ensure that women and girls with epilepsy who are prescribed sodium valproate are fully informed about the risks. No additional funding is required for the NHS to make this happen.

Epilepsy Society and Epilepsy Action would like the NHS to consider the following:

- a national audit or register of all women with epilepsy so as to identify those who are taking sodium valproate and to initiate an annual review.
- discussions with women taking sodium valproate are made mandatory or incentivised through the development of an enhanced service specification. Our colleagues at Epilepsy Action have pointed out that, since the retirement of the QOF indicator for preconception counselling, there is no formal incentive for clinicians to discuss these issues with relevant patients. When the QOF indicator was in place, a 2013 survey highlighted that around a third of women had not received information about pregnancy and the associated issues.. In 2016, after the QOF indicator was retired, almost half of women said they had not been

made aware of the potential risks. This suggests that this sort of intervention does have a positive impact. An enhanced specification would equate to very few women per GP practice and could replicate models such as those for vaccination programmes for pregnant women.

- GP systems should enable coding of women within the relevant age group who take sodium valproate to enable this data to be extracted and regularly monitored.
- where a GP is issuing a repeat prescription for sodium valproate, a flagging system should incentivise him/her to take a short e-learning course about sodium valproate.
- a robust checklist that must be completed before any woman is prescribed sodium valproate.
- routine checks such as family planning appointments, should also include discussion with relevant women and girls about the risks of sodium valproate.

# Submission to the Cumberlege Review Concerning the Safety of Medicines and Medical Devices in the UK on behalf of the Organisation for Anti-Convulsant Syndrome (OACS Charity) and #FACSAware

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## Prepared in consultation with:<sup>1</sup>

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Dr Rebecca Bromley

20<sup>th</sup> April 2018



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<sup>1</sup> **Appendix G** provides the reader with a brief biography for all of those involved in the preparation of this submission.

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## The Scope of this Submission

This submission is made on behalf of the Organisation for Anti-Convulsant Syndrome (known as **OACs**), the Foetal Anti-Convulsant Network (known as **#FACSaware**) and the individuals and families that both groups represent.

An outline of the essential work undertaken by these groups is provided below.

This submission is made to Baroness Cumberlege in her role as chair of the Government ordered Review announced by the Secretary of State for Health, Jeremy Hunt, on 21 February 2018<sup>2</sup>. The purpose of this Review is to consider – in the context of medicinal products/devices identified as, **Primodos**, **Sodium Valproate** and **Vaginal Mesh**:

- *‘Firstly, the robustness and speed of the processes followed by the relevant authorities and clinical bodies to ensure that appropriate processes were followed when safety concerns were raised;*
- *Secondly, whether the regulators and NHS bodies did enough to engage with those affected to ensure their concerns were escalated and acted upon;*
- *Thirdly, whether there has been sufficient co-ordination between relevant bodies and the groups raising concerns; and*
- *Fourthly, whether we need an independent system to decide what further action may be required either in these cases or in the future’.*

Mr Hunt explained; *‘This is because one of the judgments to be made is whether, when there has been widespread harm, there needs to be a fuller, or even statutory, public inquiry. Baroness Cumberlege will make recommendations on the right process to make sure that justice is done and to maintain public confidence that such decisions have been taken fairly’.*

This submission relates to Sodium Valproate. It aims to help Baroness Cumberlege to consider these focal issues as they relate to Sodium Valproate.

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<sup>2</sup> <https://hansard.parliament.uk/commons/2018-02-21/debates/7DA2E2F3-E1E6-40CB-8061-680E0399CA97/MedicinesAndMedicalDevicesSafetyReview>

## The Purpose of this Submission

It is now well established by clinical researchers, in medical literature and across the regulatory community that Sodium Valproate is a teratogen; and that children exposed to this drug in utero suffer an increased risk of physical, developmental and neurological injuries. That cluster of injuries is known as 'Foetal Valproate Syndrome' (**FVS**).

With adequate warnings directed at both the users of Sodium Valproate preparations and their treating clinicians, FVS was, and is, an almost entirely avoidable injury. Yet, as at the date of this submission, as many as 20,000<sup>3</sup> individuals in the UK have been diagnosed with (or may suffer from) FVS.

In our submission the persistence of FVS as a diagnosis in the UK, and the number of individuals affected, is evidence of a long history of regulatory and legal failure in the prescription of Sodium Valproate as an anticonvulsant in the UK.

Those affected by FVS continue to pay the highest price for that failure:

*'I am mourning my child now and will be mourning the death of her when she's gone, this is the result of Valproate, no parent wants to see their child slowly die in front of them'*<sup>4</sup>

They do so without any acknowledgment on the part of the manufacturer or regulator of the role that they have played in creating and perpetuating the incidence of FVS in the UK; and crucially they do so without compensation.

Against that backdrop, this submission sets out; the legal case for a Public Inquiry into the regulatory and legal failings exposed by FVS and describes both the urgent need, and moral imperative, for compensation to be paid to all those affected by FVS in the UK.

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<sup>3</sup> <https://www.epilepsyresearch.org.uk/nearly-20000-children-harmed-by-epilim-sodium-valproate/> and <https://hansard.parliament.uk/Commons/2017-10-19/debates/84D4BB19-D2BF-446A-A249-CD28BD7E8E06/ValproateAndFoetalAnticonvulsantSyndrome>: This figure is arrived at through research undertaken by Rebecca Bromley, details of which can be provided to the Review upon request.

<sup>4</sup> See contributions from those affected by FVS at **Appendix A**.

To achieve that purpose this submission is divided into 3 chapters:

- **Chapter 1;** provides the background on the clinical history and impact of Sodium Valproate in the UK;
- **Chapter 2;** sets out the legal case for a Public Inquiry and is focussed upon dealing with the first three issues raised by Mr Hunt in his announcement on 21<sup>st</sup> February 2018: These are the Governmental, regulatory and legal failings that have resulted in FVS and have necessitated the 40-year old campaign for justice led by groups such as OACS Charity and FACSaware.
- **Chapter 3;** sets out the moral imperative for the creation of a Compensation Fund, identifying the clinical and psychological needs of those affected by FVS and possible mechanisms through which such compensation could be awarded.

## Introduction to the Organisations behind this Submission

### **OACS Charity**

The Organisation for Anticonvulsant Syndromes is a registered charity based in the UK (**OACS Charity**). The charity was set up in 1999 to provide support and raise awareness for children affected by Fetal Anticonvulsant Syndromes (**FACs**) including Fetal **Valproate** Syndrome (or **FVS**); and other syndromes caused by anticonvulsant or antiepileptic drugs (**AEDs**).

*OACS Ireland* is a branch of OACS UK; it has a similar remit, and provides support and representation of families in Northern Ireland and Southern Ireland.

OACS Charity's work involves advocacy, signposting and support for members. They hold regular family meetings and have a network of local coordinators around England, Wales and Scotland and a private Facebook group which acts as a secure forum. Until recently they had a youth advocate, and have a strong network of young adults who are now working to make their mark in the charity. Alongside this work, OACS Charity raises awareness through traditional and social media.

They regularly work with all the prominent specialists in the field on research projects as a patient group. OACS Charity has considerable influence now in stakeholder groups both nationally, with the MHRA and with local services. Internationally they work with the European Medicines Association (**EMA**) and, in this role, contributed to the first public hearing into the safety and efficacy of a drug within Europe.

OACS Charity is a patient led group; and its board members and volunteers are families affected FVS and FACs. The OACS Board has a rotating membership and volunteer group, the majority of members are carers for disabled children and so individuals come and go as their caring needs change.

OACS Charity was also the lead charity in the FAC litigation 2004-2010 and since then has built momentum working with other groups in a collaborative manner. OACS Charity has strong links with victim groups across Europe as they are becoming more aware of the issues.

OACS membership is not exclusive and many members also participate with other campaign groups such as FACSaware, Justice for FACS Kids and Valproate Victims UK.<sup>5</sup>

## **FACSaware**

**#FACSaware** is an online awareness campaign set up by the Fetal Anti Convulsant Trust. Reports are written for media, regulators and politicians and are based on views expressed through their networks. These reports are shared publicly on the FACSaware Facebook page.

It is not a registered charity and has no board or bank account.

It does not claim to provide medical advice; but by sharing experiences, the network aims to inform and support those affected by FVS; including signposting services that may be useful or of interest.

FACSaware does not have formal membership, or claim to represent all those affected. The network was launched in 2013 with a demonstration outside the MHRA offices.

Further details can be found online by searching for #FACSaware.<sup>6</sup>

As set out in **Section 15** of this submission, members of both groups have worked with Norman Lamb MP, the APPG, the EMA PRAC and the MHRA Valproate Stakeholders Network, to push for better labelling of Sodium Valproate preparations as set out in **Section 3** and to develop resources to better enable women to make informed choices about AEDs and reduce the incidence of FVS in the UK and beyond.

At **Appendix A**, members of both groups, have provided case studies describing the impact of FVS on the children affected, and the wider family unit. These case studies are not exhaustive but are offered as 'snapshots' of the long term effects of this drug. These are the 'real life' accounts of those for whom FVS isn't a legal problem or a catalogue of regulatory

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<sup>5</sup> <https://www.oacscharity.org/>

<sup>6</sup> <http://www.facsaaware.net/>

failings but a day to day reality. It is important to remember that for the vast majority of those who care for individuals with FVS they also have to deal with their own epileptic condition.

The bravery and dignity of those who have shared their experiences through OACS Charity and FACSaware is self-evident. As is their justified anger:

*'...these children and families have been let down not just by Sanofi but by the Government, by the system, by the NHS, fighting for basic care, disability benefits, chasing professionals, it's pretty disgraceful, we as a family have been put through hell, called liars told we are fabricating our daughter's condition....the ignorance and lack of education surrounding this catastrophic, debilitating rare disease is as bad as the disease itself, knowing this man made condition could have been stopped is heart-breaking<sup>7</sup>'.*

*'...I still carry the guilt of having taken the drug that harmed my children, with knowledge, I could have made different choices. More than anything I feel anger and a sense of loss for the lives we could/should have had instead of the daily struggle we have instead<sup>8</sup>'.*

**The question of how to respond to and improve that experience is entrusted to this Review.**

A summary of the expertise of those who have assisted these groups with the preparation of this submission is provided in **Appendix G** of this document.

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<sup>7</sup> See contributions from those affected by FVS at **Appendix A**.

<sup>8</sup> As above.

## Executive Summary

- Sodium Valproate medicines are used to treat various conditions such as epilepsy, the manic phase of bipolar disorders (since 2009) and severe migraines (this application is off label use in some EU countries).
- In the UK the primary use of Sodium Valproate is, and has always been, in relation to epilepsy as an anticonvulsant (**AED**).
- There is little doubt that Sodium Valproate is an effective medication in treating patients at risk of epilepsy associated convulsions.
- Sodium Valproate is marketed internationally under a range of brand names. In the UK, **Epilim** is by far the most dominant Sodium Valproate preparation available.
- Epilim was first licensed for usage in the UK in 1973. The company responsible for manufacturing and marketing the drug in the UK is now known as **Sanofi**.
- It is now accepted across the clinical and regulatory community by, for example, the National Institute for Health and Clinical Excellence (**NICE**), the MHRA and European Medicines Agency (**EMA**) that Sodium Valproate is a teratogen and that wherever possible prescription should be avoided in female patients of childbearing age.
- The congenital birth defects associated with in utero exposure to Sodium Valproate include:
  - Neural tube defects (NTDs), such as spina bifida
  - Cleft lip and palate
  - Facial and skull malformations
  - Heart, kidney, urinary tract and sexual organ malformations
  - Limb defects
  - Developmental delay
  - Autism Spectrum Disorders (ASDs)
  - Attention Deficit Hyperactivity Disorder
  - Ear malformations and auditory processing
  - Skeletal malformation
  - Arthritis in older children
  - Effects on the endocrine system
  - Sexual identity problems (which occur due to a mismatch between genital development and neural / sexual identity development).

- Psychomotor issues.
- Withdrawal symptoms – associated with prenatal Sodium Valproate exposure.

It is important to understand that this list is not exhaustive.

- When these congenital abnormalities, either singularly or in combination, are identified in children exposed to Sodium Valproate in utero they are diagnostic signifiers of **FVS**.
- The controversy surrounding Sodium Valproate is focused upon the teratogenic potential of the drug and the historic failure of the regulator and manufacturer to communicate that potential to clinicians and patients.
- It is submitted that by the early 1980s the regulator/manufacturer was in possession of sufficient information to conclude that Sodium Valproate was a teratogen which increased the risk of congenital abnormalities above the risks associated with epilepsy in general or where alternative AEDs were used.
- However, this information was not communicated directly to patients until as late as 2005; whilst, in our submission, appropriate care pathways for women of child-bearing age using Sodium Valproate were not instituted by the regulator/manufacturer until as late as 2016.
- That failure of the regulator/manufacturer constituted a dereliction of their statutory duties under the Medicines Act 1968, and successive legislation, to safeguard patients and warn of the adverse risks associated with medications.
- That failure also created a fundamental '**Information Gap**' between regulator/manufacturer-clinician/patient out of which the tragedy of FVS has developed.
- An info-graphic describing this '**Information Gap**' is provided at **Appendix B** and in Chapter 2 of this submission. The case for a Public Inquiry into medical product regulation in the UK is made with reference to the creation and maintenance of this 'Information Gap' which is exposed through the history of FVS in the UK.
- Those affected by FVS and their families have complex care needs and are in the unusual position of having to cope with children with often profound disabilities whilst dealing with the fact of their own epileptic and or mental health condition.
- For many of the mothers with epilepsy who are caring for children affected by FVS, stress is a trigger for their epileptic convulsions; the fact that they have been unheard and uncompensated for so long, despite their persistent campaigning, has often exacerbated their own clinical condition – this has added injury to injury.

- We describe, in **Section 15**, the **Double Disability** which the mothers of FVS children experience; the fact of their own epilepsy in addition to the problems experienced by their children with FVS, a condition brought about by the Epilim which has enabled them to live normal lives. This imposes a significantly greater burden on these women than would be the case if they did not suffer from epilepsy.
- Setting aside the emotional and psychological costs; the physical care needs of those affected by FVS place significant financial demands on the individual families affected and upon the NHS and/or Local Authority, who have been left to shoulder the significant cost burden associated with FVS.
- Sanofi, the manufacturer responsible for Sodium Valproate, has made very significant profits as a result of its marketing of Sodium Valproate in the UK without shouldering any of the consequential costs of FVS injuries.
- Litigation initiated against Sanofi on behalf of those affected by FVS and their families was discontinued when the Legal Aid Agency decided to withdraw legal aid funding in 2010, three weeks before Trial: Consequently, FVS sufferers have been denied access not only to compensation but also the opportunity to bring the fact of the manufacturer's and regulator's failures into the public domain.
- This contrasts with the experience of FVS sufferers in other jurisdictions.
- In 2016 the French Government instituted payments to FVS sufferers through a centrally constituted Compensation Fund.
- The recent reparative actions of the French Government in respect of FVS, contrast with the historic inaction of successive UK Governments: This contrast is noteworthy given that both jurisdictions have had to deal with:
  - the same drug (Sodium Valproate)
  - the same injuries (FVS)
  - the same manufacturer (Sanofi); within
  - the same legislative framework- by virtue of the European wide Product Liability Directive.
- The scale of the task of compensating UK **FVS** sufferers is hard to estimate; however, the moral imperative to facilitate such compensation is abundantly clear:

*'I can tell you from my experience of 32 years that there has never been enough support/facilities within the community to cover the needs of my daughter or any other person with learning difficulties/special needs or disabilities. There has been a continuous lack of understanding of the complexities of FVS<sup>9</sup>*

- In summary, this submission seeks the following outcomes:
  - A compensation and care package for all those affected by FVS;
  - A Judge led Public Inquiry into the regulation and licensing of medical products within the UK, focussing upon FVS as a case study; and
  - Scrutiny of how consumers can be better safeguarded and, if necessary, compensated, in a revised regulatory framework post-Brexit.

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<sup>9</sup> See contributions from those affected by FVS at **Appendix A**.

## Chapter 1: A Statement of Facts

### Section 1: The Clinical History of Sodium Valproate in the UK

Baroness Cumberlege will have access to a substantive set of resources documenting the full clinical profile and history of Sodium Valproate prescription in the UK. At the date of this submission, the authors only have access to documents within the public domain. Within those limitations we set out below the most salient aspects of the clinical history of Sodium Valproate in the UK.

#### *Clinical History*

Sodium Valproate was first produced, as a chemical compound, in 1881 and came into medical use in 1962. Sodium Valproate medicines have been approved for use in the EU since 1967 as an anticonvulsant therapy, and have been licensed for use in the UK since 1973<sup>10</sup>.

The manufacturer with initial responsibility for introducing Sodium Valproate into the UK, branded as **Epilim**, was Reckitt-Labaz. In or around 1980, Reckitt-Labaz was acquired by the UK division of French parent company Sanofi Synthelabo who have maintained ownership of the Epilim brand ever since, whilst acquiring pharmaceutical competitors Aventis and Genzyme, and simplifying the company name to **Sanofi**<sup>11</sup>.

Sodium Valproate medicines are used to treat various conditions such as epilepsy, the manic phase of bipolar disorders (since 2009)<sup>12</sup> and severe migraines (this application is off label use in some EU countries). However, in the UK the primary use of Sodium Valproate is, and has always been, in relation to epilepsy as an anticonvulsant ('**AED**'). For a number of years it was perhaps the most effective AED on the market and even today for some patients prescribed

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<sup>10</sup> Scott, D.F. (1993). The history of epileptic therapy : an account of how medication was developed

<sup>11</sup> A summary of Sanofi's corporate history is available here: <http://www.sanoficareers.co.uk/about-us/our-history>

<sup>12</sup> EMA PRAC Meeting 25-29 September 2017  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/events/2014/03/event\\_detail\\_00926.jsp&mid=WC0b01ac058004d5c3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/03/event_detail_00926.jsp&mid=WC0b01ac058004d5c3)

this medication it is the only form of effective treatment. Since the early 1980s the effect of the drug has become far better understood; since at least the mid 1990's has there been sufficient understanding of those effects to mandate alternative treatment for pregnant women with epilepsy, or those aiming to conceive.

Effective alternative preparations are available for most women with epilepsy, and in line with updated regulatory practice must now be offered to women of child-bearing potential who require AEDs.

Off label treatments include the prescription of Sodium Valproate for conditions such as low mood.

The drug is marketed internationally under several brand names, including Depakote, Depakine and Epilim<sup>13</sup>. In the UK, Epilim is by far the most dominant Sodium Valproate preparation available. A list of the various brand names and formulations of Sodium Valproate as a medical preparation are listed in **Appendix C**, along with the manufacturers who produce these formulations.

#### *The Teratogenic Effects of Sodium Valproate*

There is little doubt that Sodium Valproate is an effective medication in treating patients at risk of epilepsy associated convulsions.

The efficacy and importance of Sodium Valproate for the control of epileptic symptoms was recognised very shortly after its introduction to the UK market. By 1975, Sodium Valproate was positioned as a 'first line' therapy in many countries around the world. The BMJ captured the mood of some practitioners with rare hyperbole describing how Sodium Valproate had been greeted by some clinicians as '*the best thing since Greta Garbo*'. This efficacy is born out by more recent publications, including the publication of a first randomised study of anti-convulsant medications in 2007 which concluded that Sodium Valproate was the most effective; and in a survey reported in 2016, Sodium Valproate, in its various branded, forms was the most prescribed anti-epileptic drug (AED) in the world<sup>14</sup>. Indeed, as at the date of this

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<sup>13</sup> See NICE BNF Guide - <https://bnf.nice.org.uk/drug/sodium-valproate.html>

<sup>14</sup> NY Times, 3.9.2016.

submission, Sodium Valproate remains the AED of choice amongst clinicians treating patients with the most intractable epilepsies even amongst women of childbearing age<sup>15</sup>.

In this context it is important to understand that the controversy surrounding Sodium Valproate focusses not upon the direct biological impact upon adult users, but rather upon the in utero impact of the drug and its potential harm to the children of mothers with epilepsy who are prescribed the drug, particularly in high dosages (over 1000mg per day) during pregnancy or in combination with other drugs as part of a polytherapy.

The European Medicines Agency (**EMA**) Pharmacovigilance Risk Assessment Committee (**PRAC**) unanimously agreed in September 2017 that the teratogenic potential of Sodium Valproate increased the risk of fetal abnormality and that the nature of that risk was now *“undeniable and well characterized”*<sup>16</sup>.

The Medicines and Health Care Regulatory Agency (**MHRA**) currently reports that whilst the overall risk in the population of fetal abnormality is 2-3% of all viable births, in women taking Sodium Valproate this risk is increased to around 10%. As such, for women taking Sodium Valproate at the time of conception their unborn children have a 3-5 fold increased risk of fetal abnormality. This risk of abnormality increases when neurodevelopmental, as well as physical, disabilities are included. Available data indicates that up to 40% of babies born to women taking Sodium Valproate are at risk of developmental issues and up to 10% are at risk of physical disability<sup>17</sup>.

Notably, **Bromley 2013**<sup>18</sup>, showed an increase in the risk of neurodevelopmental disorders in children exposed to monotherapy Sodium Valproate (6/50, 12.0%) and in those exposed to polytherapy Sodium Valproate (3/20, 15.0%); compared to ‘control children’ within the study (4/214; 1.87%). The incidence of neurodevelopmental disorders amongst the

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<sup>15</sup> ABN Statement on the use of Sodium Valproate in Pregnancy, accessed 22.3.18: <https://www.theabn.org/resources/abn/a/abn-statement-on-valproate.html>

<sup>16</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2017/10/WC500236051.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/10/WC500236051.pdf)

<sup>17</sup> <http://researchbriefings.files.parliament.uk/documents/CDP-2017-0186/CDP-2017-0186.pdf>

<sup>18</sup> Bromley 2013, The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115188/>

'control children' within the study was noted to be comparable with incidence in the general population of reportedly 1% in the UK. As such, this study indicates a 12-15 fold increased risk of neurodevelopmental disorders in children exposed to Sodium Valproate in utero. **Autistic Spectrum Disorder (ASD)** was the most frequent diagnosis in children exposed to Sodium Valproate within the study. By contrast, no significant increase was found amongst children exposed to other anticonvulsants such as carbamazepine (1/50) or lamotrigine (2/30).<sup>19</sup>

Anthony Marson, editor of the Cochrane Epilepsy Group, has led two major systematic reviews assessing the developmental outcomes and malformation rates following in utero exposure to antiepileptic drugs. He advises that wherever possible, Sodium Valproate must be avoided in pregnancy and that there is no reason to prescribe Sodium Valproate to women with **focal epilepsy**<sup>20</sup> who are of child bearing age<sup>21</sup>.

This submission does not set out a full survey of the data which establishes the teratogenic potential of Sodium Valproate on the basis that this has now been accepted by both the MHRA and the EMA. A central concern for a Public Inquiry will be to undertake both; a comprehensive review of the literature on Sodium Valproate; and discussions with the MHRA and Department of Health; in order to chart the recognition over time of those risks whilst assessing whether those risks should have been recognised and publicised any earlier by both manufacturer/regulator. Those responsible for this submission have produced the infographic at **Appendix B** which relates to the alleged disconnect between knowledge held by the regulator/manufacturer and what was communicated to the patient.

At **Appendix C** we have included a list of recent (post 2010) FVS literature. This includes two Cochrane Collaboration Reviews<sup>22</sup> which look back over the literature to that point and confirm findings, as well as new work which extends understanding of particular effects.

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<sup>20</sup> Note that Sodium Valproate remains the drug of first choice for 'generalised onset' epilepsy as opposed to 'focal epilepsy': These terms refer to different classifications of seizure which are explained here: <https://www.epilepsy.org.uk/info/seizure-classification>

<sup>21</sup> EMA PRAC Meeting Sept 2017 – Page 38  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2017/10/WC500235902.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/10/WC500235902.pdf)

<sup>22</sup> 'Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child' **Bromley** et al : Cochrane Database : 2014 :Issue 10 : CD010236 and ' Monotherapy treatment of epilepsy in

We are grateful to **Professor Peter Turnpenny of University of Exeter Medical School** for preparing this list for us.

### *Foetal Valproate Syndrome (FVS)*

The congenital birth defects associated with in utero exposure to Sodium Valproate include:

- Neural tube defects (**NTDs**), such as spina bifida
- Cleft lip and palate
- Facial and skull malformations
- Heart, kidney, urinary tract and sexual organ malformations
- Limb defects
- Developmental delay
- Autism Spectrum Disorders (**ASDs**)
- Attention Deficit Hyperactivity Disorder
- Ear malformations and auditory processing
- Skeletal malformation
- Arthritis in older children
- Effects on the endocrine system, and sexual identity problems which occur due to a mismatch between genital development and neural / sexual identity development.
- Psychomotor issues
- Withdrawal symptoms – associated with prenatal Sodium Valproate exposure

These injuries, singularly or in combination, when linked to in utero exposure to Sodium Valproate and when other causes are excluded, may be described as Foetal Valproate Syndrome or **FVS**<sup>23</sup>.

This list is not exhaustive and research continues.

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pregnancy: congenital malformation outcomes in the child': **Weston** et al: Cochrane Database : 2016 : Issue 11 : CD0102200

<sup>23</sup> See Yunos 2017, as per Fn 27

Dr Rebecca Bromley, Research Fellow, University of Manchester, responding to queries emailed to her for the purpose of drafting this submission has noted the following:

*'The vast majority of research completed is into the risks associated with valproate by taking cohorts of children with a history of valproate exposure and comparing their outcomes (physical or neurodevelopmental) to a control group or a group exposed to another anti epileptic drug. Research into children with actual FVS (diagnosed appropriately) is extremely lacking. However, the increased level of risk seen in cohorts with a history of valproate exposure, once the background risk has been taken into consideration, are seen as being associated with the valproate exposure and therefore likely to represent children with probable FVS. It should be considered that the rates of malformation and neurodevelopmental difficulties will be lower in these cohorts as not every child will be affected by the exposure. Currently, we do not know for example the true prevalence of major malformation rate in children with clinically diagnoses FVS. We know that it is around 10% in children with a history of valproate exposure (or as high as 24% if the dose is high) but the rate will be even higher if you took a cohort of individuals with confirmed valproate embryopathy (e.g. fetal valproate syndrome). FVS is a constellation of physical and neurodevelopmental symptoms and is only diagnosed when other causes of those symptoms have been excluded'.<sup>24</sup>*

#### *How long have these effects been known about?*

Since it is anticipated that the Review will seek relevant guidance from clinical experts regarding the foetal impact of Sodium Valproate, the information set out under this subheading is provided by way of introduction and overview only.

From as early as **1978**, Sodium Valproate has been associated, in the published medical literature, with congenital abnormalities in the children of women with epilepsy treated with this drug during pregnancy. The spectrum of abnormalities attributed initially were physical in nature, later studies have better elucidated the neurological/developmental delay in those children.

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<sup>24</sup> Email correspondence Dr Rebecca Bromley, Research Fellow, University of Manchester, to Sarah Moore at Leigh Day 19.4.18.

“Foetal Sodium Valproate Syndrome” (FVS) was first described in 1978 by **Hanson et al**<sup>25</sup>, defining the characteristic features of a teratogenic response to Sodium Valproate from the distinct cranial appearance of children exposed to Sodium Valproate.

In a letter to the editor of the Lancet in **1980**<sup>26</sup>, three physicians from the George Washington University Medical centre set out their findings following evaluations of valproic acid testing in animals and concluded that it was equal in teratogenic harm to trimethadione<sup>27</sup>. They noted that published clinical data only showed a fetal abnormality in 1 of 13 children born to mothers using Sodium Valproate during pregnancy. They noted that:

*“Since many women of childbearing age must have been treated with the drug since its introduction 10 years ago, one would expect considerably more information than has been published. We would be interested to hear from any of our colleagues who have had experience of valproic acid during early pregnancy.”*

Further information concerning the teratogenic potential of Sodium Valproate appears to have been made available to the US medical community from **1982** onwards. During 1982/3, Abbott Laboratories, the US manufacturer of Sodium Valproate formulation ‘Depakote’, issued a ‘Dear Dr Letter’. This letter warned US clinicians of the known risk of spina bifida in children prenatally exposed to Sodium Valproate.

In January **1983** the UK’s Committee on Safety of Medicines<sup>28</sup> identified Sodium Valproate under their “Current Problems”. It noted that over the previous fifteen years, there had been several epidemiological studies identifying an increase in the incidence of congenital malformations in children born to mothers with epilepsy. In more recent surveys, the occurrence of malformations was higher in epileptics using anticonvulsant therapies. They noted the risk of a baby being born with malformations to a mother taking anti epileptic therapy

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<sup>25</sup> Hanson, J.W. & Smith, D.W. The fetal hydantoin syndrome. The Journal of Pediatrics

<sup>26</sup> The Lancet, March 22 1980

<sup>27</sup> Trimethadione is an oxazolidinedione anticonvulsant. It is most commonly used to treat epileptic conditions that are resistant to other treatments. If administered during pregnancy, fetal trimethadione syndrome may result causing facial dysmorphism (short upturned nose, slanted eyebrows), cardiac defects, intrauterine growth restriction (IUGR), and mental retardation. The fetal loss rate while using trimethadione has been reported to be as high as 87% - Teratology and Drug Use During Pregnancy Retrieved January 2007

<sup>28</sup> Current Problems, Committee on Safety of Medicines, Issue 9, Jan 1983

to be 1 in 10. The report stated that only 1 paper was available for reference at that time of publication which demonstrated a clear teratogenic effect in humans. Folic acid was advised as a treatment during pregnancy and it was postulated that there may be a case for withdrawal of anticonvulsants during pregnancy in suitable patients with minor epilepsy conditions.

One of the most significant papers by **DiLiberti et al 1984**<sup>29</sup>, evaluated the effects of Sodium Valproate in 7 children that had been exposed to its use in utero. They observed consistent facial changes in all 7 children and additional abnormalities in 4 of the 7. They characterised the deformities as follows:

*“The facial changes consisted of epicanthal folds which continued inferiorly and laterally to form a crease or groove just under the orbit, flat nasal bridge, small upturned nose, long upper lip with a relatively shallow philtrum, a thin upper vermilion border, and downturned angles of the mouth. Hypospadias, strabismus, and psychomotor delay were found in two males; two children had nystagmus and two had low birth weight.”*

A full publication by **Robert et. al**<sup>30</sup> in **1986**<sup>31</sup> provided still more robust data. The authors reviewed 148 pregnancies in identified epileptic women from 2 distinct sources: (1) questionnaires sent to a group of women, 15–45 years old, having had an EEG between 1976 and 1983 to establish pregnancy; and (2) a computerized registry involving all pregnancies occurring in 3 maternity wards in Lyon between 1979 and 1983. The study reported that within the sample, the most common drug regimen during early pregnancy was monotherapy. The most commonly used drug was phenobarbitone (67% of cases) followed by valproic acid (25% of cases). The study observed 26 physically malformed infants (17.7%). Among them, 18 (70%) had minor defects only. No major malformation was observed in the ‘no drug’ group. The study did not assess neurodevelopment abnormalities.

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<sup>29</sup> John DiLiberti, 1984 The Fetal Valproate Syndrome, American Journal of Genetics

<sup>30</sup> <https://www.karger.com/Article/Abstract/116048>

<sup>31</sup> Following a preliminary report in France MMWR Weekly and a letter in ‘The Lancet’ (1983) ;1142 ‘Valproate and birth defects’ Robert E and Franz R

In a paper by Ardinger et al 1988<sup>32</sup>, the authors aimed to verify the term Fetal Sodium Valproate Syndrome (FVS). Their work showed no consistent alterations of pre or post natal growth with exposure to Sodium Valproate monotherapy however, when used in combination with other anticonvulsants, postnatal growth deficiency and malformations were present.

An abundance of literature reporting on cohort studies was released in 1988-1995, all of which documented the effects of Sodium Valproate treatment on babies born to mothers taking the drug during pregnancy. A comprehensive literature review can be made available if required.

In their 1995 paper, Clayton-Smith et al<sup>33</sup> summarised the known clinical features of Foetal Valproate Syndrome as:

*“Neural tube defects; congenital heart disease; cleft lip and palate; genitourinary malformations; tracheomalacia; radial ray defects; arachnodactyly/overlapping digits; Abdominal wall defects”*

Espinasse et al 1996<sup>34</sup> (originally published in French) summarises the effects of Sodium valproate as:

*“The teratogenic effects of valproate are now established (anomalies of closure of the neural tube, tetralogy of Fallot, cleft lip, characteristic anomalies of the face). **These effects remain, however, insufficiently known by prescribers. (...) Conclusion: all epileptic mothers treated should be warned of the teratogenic risk of valproate during pregnancy, such that treatment can potentially be reviewed**”* [emphasis added].

Against this backdrop a UK Pregnancy and Epilepsy Register was established in **1996** in order to collate information concerning AEDs prescribed, treatment regimes (mono or poly therapy)

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<sup>32</sup> Ardinger, 1988, Verification of the Fetal Valproate Syndrome Phenotype, American Journal of Medical Genetics

<sup>33</sup> Clayton-Smith J, Donnai D. J Med Genet 1995 32:724

<sup>34</sup> M Espinasse, S Manouvrier, 1996 Embryofœtopathie au valproate : une pathologie encore trop mal connue. À propos de quatre observations Fetal valproate syndrome: four new cases, Archives de Pédiatrie  
Volume 3, Issue 9, September 1996

and incidence of major congenital malformations (**MCM**) during the first 3 months of life.

Results from this Register were published in **2005**. The data was based on over 3600 cases, the overall MCM rate was 4.2% rising to 6% where polytherapy was used. This compared with an MCM rate of 3.5% in epileptic women who had taken no AED during pregnancy. Where the AED was Sodium Valproate the MCM rate rose to 6.2%, significantly this was 3 times higher than the MCM rate reported in patients prescribed carbamazepine (just 2.2%). For women on Sodium Valproate dosages of more than 1000mg per day, the MCM risk rose to 9.2%. It is important to note that MCM, within the definition of the Register, as at 2005, did not include developmental delay or cases of FVS which were defined as 'minor' rather than major congenital malformations<sup>35</sup>. Inclusion of these cases would have increased the congenital malformation incidence rate versus the 'no AED' group many fold.

In 2006, "Foetal Valproate Syndrome of Valproate acid", published by the Journal of Paediatrics in 2006, referenced a study by **J. Kozma**<sup>36</sup> stating:

*"In a total of 69 cases of FVS, the majority of patients had musculo-skeletal anomalies (62%), others were minor skin defects (30%), cardio-vascular anomalies (26%), genital anomalies (22%), pulmonary anomalies (16%) and neural tube anomalies (3%). Anomalies of the brain, the eyes, the kidneys and of hearing were found less frequently. 15% of the patients had growth retardation. 12% of the affected children died at a young age and 29% of patients had survived the developmental defects / mental deficiency".*

**Yunos et al 2017**<sup>37</sup>, reported a retrospective study of 29 reported cases in Ireland of FVS diagnosed between 1995-2016 (21 years). This study again showed the same common features as described in the early literature referenced above:

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<sup>35</sup> P.7, Morrow et al., 2005, Malformation risk of AEDs in pregnancy:

<http://www.cardiffandvaleuhb.wales.nhs.uk/sitesplus/documents/1143/MalformationRisks%20of%20AEDs.pdf>

<sup>36</sup> "Valproate acid embryopathy: report of two brothers and sisters, a new expansion of phenotypic anomalies and a literature review" Am. J. Med. Genet 2001

<sup>37</sup> Fetal valproate syndrome: the Irish experience, Hamizah Mohd Yunos, 23 January 2018, Royal Academy of Medicine in Ireland 2018

*“Features commonly described are prominent metopic ridge, midface hypoplasia, epicanthic folds, micrognathia and broad and flat nasal bridge. Four (13.7%) had cleft palate, three (10%) had neural tube defect, four (13.7%) with cardiac malformation, 15 (52%) experienced developmental delay including six (40%) with speech delay, 11 (38%) with limb defects, four (13.7%) reported with neurodevelopmental disorder and two (7%) had hypospadias”*

In the conclusion to their 2017 publication, the authors advise:

*“FVS is still seen in the Irish population even though the teratogenicity of the VPA has been known for over 32 years. It is very important to create public and professional awareness to prevent FVS whenever possible.”*

The causal mechanism of FVS remains unknown at the date of this submission. Reference is drawn to the 2016 **Nie et al**<sup>38</sup> paper at Figure 1, which demonstrates the various hypotheses to explain the teratogenic effects as:

*“There may be multiple mechanisms that lead to the formation of cognitive defects in foetuses, including ischemic condition, neural suppression, decreased folate absorption, neural apoptosis and an increase in free radical formation”*

### *Untreated Epilepsy during Pregnancy*

Epilepsy is an extremely serious and potentially life-threatening disorder. The majority of epileptic women who become pregnant will need to continue usage of appropriate anticonvulsant medications throughout their pregnancies. The risks of untreated epilepsy during pregnancy are very real and those risks include:

1. Risk of falling from uncontrolled or untreated epilepsy leading to death is 2-3 fold higher in women with epilepsy compared to the population mortality risk<sup>39</sup>.

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<sup>38</sup> Nie et al 2016, Neurological teratogenic effects of antiepileptic drugs during pregnancy – Experimental and Therapeutic Medicine 12: 2400-2404, 2016

<sup>39</sup> <http://researchbriefings.files.parliament.uk/documents/CDP-2017-0186/CDP-2017-0186.pdf>

2. Risk of mortality from untreated epilepsy in pregnant women with epilepsy is 10 fold higher than the risk of mortality in pregnant women without epilepsy<sup>40</sup>
3. Risk of death to the fetus from epileptic fits where the mother has subsequently recovered<sup>41</sup>.
4. There are further risks to the foetus if the mother were to fall when fitting or whilst in labour where the fetus may be starved of oxygen for example.

### *Alternatives to Sodium Valproate for Pregnant Epileptic Women*

For most women, particularly those with focal epilepsy, alternative therapies will be available to them during the term of their pregnancies which do not expose their unborn children to the same degree of teratogenic risks associated with Sodium Valproate. For many of the women prescribed Epilim, alternative anti-convulsant medications may have been available and appropriate, had that degree of teratogenic risk been properly appreciated.

The list provided at **Appendix E** indicates some of the alternative anti-convulsant medications available to epileptic women along with the date of first licence and what is known regarding the teratogenic potential of each preparation.

Current National Institute for Health and Care Excellence (**NICE**) guidance recommends that, wherever possible, Sodium Valproate is not given to women of childbearing age provided the patient's convulsions can be controlled with alternative preparations<sup>42</sup>. Although features of FVS have been associated with almost all of the in utero anti-epileptic drugs, there are alternative medications which, for some women, can provide effective anti-convulsant therapy without the teratogenic risks now conclusively associated with Sodium Valproate exposure in utero.

However, in this context, it is important to understand that for some patients prescribed Sodium Valproate as teenagers (epilepsy onset is often at puberty), changing medication may be problematic as attested to by one of OACs' members:

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<sup>40</sup> Barrett, Report of an Epilepsy Research foundation Workshop, 2003

<sup>41</sup> <http://americanpregnancy.org/pregnancy-complications/epilepsy-pregnancy/>

<sup>42</sup> <https://bnf.nice.org.uk/drug/sodium-valproate.html#pregnancy>

*'It is terrifying to have an epileptic fit. To feel your body be so completely out of control. Experiencing life threatening situations, and the painful recovery afterwards. My epilepsy has never been in full control so the fear of changing medication after trying so many times in hospital, left me terrified'.<sup>43</sup>*

This difficulty is also recognised by the Association of British Neurologists, who explain the problem as follows<sup>44</sup>:

- Firstly, there is no certainty that the alternative treatment will be as effective for her epilepsy. For women who are seizure-free, this might mean loss of driving privileges, renewal of social stigma, loss of confidence, and threat to work and education;
- Secondly, a change in medication from one that is effective to one where control is less certain might allow recurrence of generalised convulsive seizures, with a real risk of causing epilepsy-related death;
- Thirdly, the Driver and Vehicle Licensing Agency (DVLA) advises drivers who change their antiepileptic medication to stop driving from the start of any change until six months after its completion. Clearly this may have a significant impact on a patient's lifestyle and/or employment options.

These factors underscore the importance of ensuring that information about the teratogenic capacity of Sodium Valproate is communicated to clinicians and patients **as fully and as early as possible**.

We note that the MHRA has now changed the license for Valproate in the UK following the 2017 EMA review into Valproate as described further in **Section 3** below. Valproate is no longer to be prescribed to females of childbearing potential unless;

- All other AEDs are ineffective or not tolerated;
- The patient has signed an Acknowledgement of Risk Form; and
- Is on a Pregnancy Prevention Programme.

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<sup>43</sup> See contributions from those affected by FVS at **Appendix A**.

<sup>44</sup> From the ABN website, accessed 22.3.18: <https://www.theabn.org/resources/abn/a/abn-statement-on-valproate.html>

This change in the license is supported by updates to the NICE guidelines, GP prescribing software and information to patients. It is understood that the MHRA webpage will carry this updated guidance from 24 April 2018.

On this basis, the extent of FVS in the children of epileptic women in the UK is, in part, the legacy of prescription of a known teratogen at a time when alternative therapies were available but the full risks of the drug were not sufficiently shared with clinicians and patients.

## Chapter 2:

### The Legal Case for a Public Inquiry: Acknowledging and Closing the ‘Information Gap’

This section of our submission focusses upon alleged failures by the UK regulatory bodies and the manufacturer of Epilim to provide:

1. Sufficient information to clinicians to enable them to properly advise patients, and
2. Sufficient information directly to patients to enable them to decide whether or not to consent to treatment;

in order to safeguard patients from the risks associated with Sodium Valproate.

This section is intended to respond to the first objective of this Review as identified by the Secretary of State, to examine:

*‘... the robustness and speed of the processes followed by the relevant authorities and clinical bodies to ensure that appropriate processes were followed when safety concerns were raised;*

In our submission, the relevant ‘processes’ were insufficiently robust and far too slow. Those failures constituted a breach of the statutory duties imposed by the (now superseded) Medicines Act 1968, which constitute the basic architecture of our current regulatory system and require the manufacturer to candidly disclose risks to the regulator; and for the regulator to ensure that these risks are properly communicated to patients and clinicians.

In failing to appropriately communicate the known risks of the teratogenic potential of Epilim to patients and clinicians, the manufacturer/regulator created an ‘Information Gap’ which is explored in this chapter of our submission and summarised in the info-graphic at **Appendix B**. This info-graphic marks key publications in terms of the way in which research into Sodium Valproate as a teratogen has developed over time. **We would like to thank Dr Rebecca**

**Bromley, Research Fellow, University of Manchester, for her assistance in identifying these key texts.**

## **Section 2: The Regulatory History of Sodium Valproate in the UK**

### *Regulation of Medicinal Products in the UK*

In order to fully understand those alleged failures it is first necessary to understand the principles of the relevant regulatory regime from 1973-2018.

In 1963, following the Thalidomide tragedy, a Committee on the Safety of Drugs (the **CSD**) was established in the UK with the intention of ensuring that UK patients were never again exposed to harmful medicinal products<sup>45</sup>. The CSD subsequently became the Committee on the Health and Safety of Medicines (**CSM**) under the terms of the Medicines Act of 1968, which provided the legal framework for the control of medicines in the UK<sup>46</sup>. In 2005 the CSM became the Commission on Human Medicines and subsequently the present Medicines and Health Care Products Regulatory Agency (**MHRA**).

Under the terms of the original Medicines Act 1968, the UK Government was given the discretion to:

- Grant or refuse manufacturers a license to sell their drugs within the UK based upon an assessment of the safety, efficiency or (efficacy) and quality of the medicine (s.19);
- Make enquiries of the manufacturer regarding any relevant clinical information, such as testing, that would better enable the Government to evaluate the safety of the product prior to licensing (s.44);
- Impose conditions upon the manufacturer in relation to the content and placement (e.g. inside the package, on the package) of any labelling information, with the objective of ensuring that such labelling was accurate and not misleading (s.85).

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<sup>45</sup> Drug Benefits and Risks International Textbook of Clinical Pharmacology, revised 2nd edition Edited by C.J. van Boxtel, B. Santoso and I.R. Edwards  
[www.who.int/medicines/technical.../tbs/Drug\\_Regulation\\_History\\_Present\\_Future.pdf](http://www.who.int/medicines/technical.../tbs/Drug_Regulation_History_Present_Future.pdf)

<sup>46</sup> <http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2031677.pdf>

These basic powers have been maintained by the Government through subsequent related Acts including the Human Medicines Regulatory Act 2012.

At a European level, the Thalidomide scandal also spurred efforts to harmonize medicinal regulation across Europe in the form of Directives 65/65/EEC, 75/319/EEC and 87/22/EEC, which through their related Regulations created the basic architecture for medicinal product harmonisation across the EU. As in the UK, a central intention of all pharmacovigilance (whether pursued under domestic or European legislation) has been to ensure that risks associated with licensed drugs are known to regulators and are communicated to clinicians and patients through accurate description of the risks associated with the product.

In more recent years there has been an increasing emphasis on clarity and candour, recently reinforced by the Supreme Court decision *in Montgomery and Lanarkshire Health Board (2015)* UKSC11, which emphasises the extent of the duty to warn of all risks in the context of obtaining appropriate patient consent in medical decision making. This decision is discussed further below.

#### *Warning of risks about Sodium Valproate in the UK*

A principal complaint of those injured by FVS, and their families, concerns the inadequate, incomplete and misleading information that was communicated directly to patients and their prescribing clinicians regarding the teratogenic potential of Sodium Valproate for more than twenty-five years.

In particular:

- Until 1997 there was no disclosure at all in the Patient Information Leaflet (**PIL**) provided to users of the nature or magnitude of the risk of teratogenesis as a result of taking Sodium Valproate.
- The PIL supplied with all formulations of Sodium Valproate (except Epilim Chrono) advised upon the necessity of medical consultation only **after** conception:

*"Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.*

- Until 2003 PILs were positively misleading in that they did not spell out the increased risk of congenital abnormalities to pregnant women with epilepsy who took Epilim, but rather suggested this was a risk shared by all pregnant women with epilepsy whether exposed to Sodium Valproate, other AEDS, or none at all.

For that reason, this section of the submission focusses upon the content and form of the information that was provided to patients and clinicians in relation to Epilim, through an analysis of the three main categories of document created by the manufacturer and authorized by the regulator under the terms of the Medicines Act 1968, and subsequent legislation.

Those documents include:

- 'Datasheets' provided to **clinicians and prescribers**<sup>47</sup>;
- 'Summary of Product Characteristics' ('**SPC's**') approved as part of the marketing process and used as the basis of information for **prescriber**. The packaging leaflets are based on the information contained in the SPC<sup>48</sup> ; and
- 'Patient Information Leaflets' ('**PILs**') which were intended to be provided directly to **patients**.

The specific product information documents reviewed in preparing this submission have been collated in a separate bundle that can be provided to the Review upon request, along with a detailed review of this documentation.

A chronological review of the product information understood to have been provided<sup>49</sup> to clinicians and patients by the regulator/manufacturer demonstrates that the information released to both groups followed two very distinctive paths; both in terms of the nature of the

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<sup>47</sup> <http://dtb.bmj.com/content/12/11/43>

<sup>48</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2012/05/WC500127919.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127919.pdf)

<sup>49</sup> Those responsible for this submission have been unable to establish which of the product information available was actually published and which was prepared by the manufacturer/regulator but not provided to clinicians/patients. This section is drafted on the assumption that all information that was prepared was provided as indicated to clinicians/patients.

information communicated and the date by which that information was communicated throughout the period 1973-2004.

Once again, this is an overview of the topic which any inquiry would review with access to the initial Licencing and subsequent Relicensing applications made by the manufacturer; examining the circumstances in which these documents were explored at the time by the Regulator and the representations about risk of injurious effect made to the Regulator by the Manufacturer against the background of contemporaneous independent research.

#### *Information provided by the Regulator/Manufacturer to Clinicians*

**From 1974-1985**, limited information regarding the teratogenic capacity of Sodium Valproate was communicated directly to clinicians through 'Datasheets' produced by the manufacturer and authorised by the regulator: 'Datasheets' during that period informed clinicians of the following:

- Under the heading of 'Precautions', 'Women of Childbearing age' were specifically identified, and prescribing clinicians were informed that:
  - *'This compound has been shown to be teratogenic in animals'*
  - *'The benefits of these compounds should be weighed against the possible hazard suggested by these findings'*
  - The teratogenic potential of Sodium Valproate was *'like certain other anticonvulsants'*.

**From 1985**, the 'Datasheets' informed clinicians for the first time that the pregnancies of women taking Sodium Valproate should be *'carefully monitored'*.

**From 1991**, the 'Datasheets' expressly identified an increased risk of congenital abnormalities for women prescribed Sodium Valproate during the course of their pregnancies but this was contextualised as a 1% increased risk of neural tube defects in particular, and as a feature of the pregnancies of epileptic women generally, i.e. irrespective of whether or not they were taking anti-convulsant medications at the date of conception and through the term of their pregnancies.

**From 1994**, the 'Datasheets' recommended monotherapy only during the course of pregnancy with dosage to be reviewed at first knowledge of the pregnancy.

**From 1995**, the 'Datasheets' expressly recommended review and maintenance of the lowest dosage necessary of Sodium Valproate during pregnancy and for the first time identified that women should be warned of the benefits and risks of taking anti-epileptic medications, i.e. not just Sodium Valproate, during pregnancy.

**From 1996**, the Specific Product Characteristic (SPC) information for Epilim Chrono 200mg identified the following specific risks associated with children not only born to women taking Sodium Valproate during pregnancy, but to epileptic women generally, '*including facial dysmorphia, neural tube defects and multiple malformations particularly of the limbs*'.

**From 1997**, the SPC information for Epilim Chrono included the following: "*In women of childbearing age, Epilim should only be used in severe cases or those resistant to other treatment.*"

**From 2001**, the SPC for Epilim Chrono set out more detailed information concerning the risk of congenital abnormalities associated with children born to epileptic women, this included women who were prescribed Sodium Valproate throughout their pregnancies, but this risk was contextualised as one to which all epileptic mothers were exposed by virtue of their condition and irrespective of whether or not they were taking anti-convulsant treatments.

**From 2003**, the SPC for Epilim Chrono set out, for the first time, the specific risks associated with Sodium Valproate, stating: '*Women of childbearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus*'.

**From 2010**, the SPC for Epilim Chrono was further updated to state: *'A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks'*

**From 2012**, the SPC for Epilim Gastro stated: *'This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a woman of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.'*

#### *Information Provided by the Manufacturer/Regulator directly to Patients*

A review of the documentation available to the authors of this submission, at the date of writing, indicates that there was no 'direct to patient' information concerning the teratogenic potential of Sodium Valproate until 1997.

**From 1997**, Product Information Leaflets (PILs) for Epilim Chrono (200mg, 300mg, 500mg) stated that epileptic women generally had a higher risk of giving birth to a child with congenital abnormalities and that mothers *'who have taken Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida'*. Patients were told, *'this however can be detected in the first part of pregnancy by normally using screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida'*. Women were advised; *'It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctors as soon as you know you are pregnant'*

**From 2003**, the PIL for Epilim Chrono (200mg, 300mg, 500mg) stated; *'Women who take Epilim during the first month of pregnancy to control their epilepsy have a small risk (1-2%) of having a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily*

*as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. There can usually be detected in the first part of pregnancy using routine antenatal screening blood tests and ultrasound scans. Rarely there may also be bleeding problems in the new born if the mother has taken Epilim during pregnancy. Infants born to mothers who took Epilim during pregnancy may develop less quickly than normal. This may also be because of the mother's epilepsy but the exact cause is not known. It is important not to stop your Epilim suddenly as this is likely to result in you having fits which may harm you and your baby"*

**From 2006**, the PIL for Epilim became more extensive, itemising the specific physical malformations associated with Sodium Valproate exposure, i.e. not just spina bifida; and for the first time included an express recommendation to consult a GP prior to becoming pregnant; to ensure use of effective contraception; and to avoid unplanned pregnancy.

**From 2010**, the PIL for Epilim was extended to include warnings regarding the risk of 'developmental delay' in infants exposed to Sodium Valproate in utero as well as the risks of physical malformation.

### **Section 3: Regulatory Interventions: MHRA, NICE and EMA**

In response to campaigners' persistent concerns, and the increasingly apparent 'information gap' between knowledge held by the regulators/manufacturers and clinicians/patients, as evidenced by the clinical data emerging from the UK Epilepsy and Pregnancy Register; the relevant regulatory bodies, from 2005 onwards, began to fulfil their regulatory responsibilities more diligently.

The publication of data from the Epilepsy and Pregnancy Register in 2005 showed:

- Pregnant women taking Sodium Valproate dosages of 1000mg+ per day were nearly 3 times more likely to give birth to a child with a major congenital malformation (**MCM**) defined as an '*abnormality of an essential embryonic structure requiring significant therapy*'; than an epileptic woman not taking any AED during pregnancy (9.2%: 3.5%);

- Pregnant women taking Sodium Valproate dosages of 1000mg+ per day were more than 4 times more likely to give birth to a child with an MCM than women taking the alternative AED carbamazepine (9.2%: 2.2%);
- These data did not include the neurodevelopmental effects of in utero Sodium Valproate exposure.<sup>50</sup>

In response to this information NICE updated their guidance to patients and clinicians in 2005 advising on the importance of:

- **Preconception counselling** for all women with epilepsy considering pregnancy.
- Increased patient awareness of the methods and consequences of prenatal screening, the genetics of their seizure disorder, the known teratogenicity of AEDs, folic acid and vitamin K supplements, labour, breast feeding, and childcare.
- Ensuring prescription of the **lowest effective dose** of the most appropriate AED, aiming for **monotherapy** where possible.<sup>51</sup>

The NICE **2005** guidance highlighted the fact of the Registry data noting in particular that Sodium Valproate was significantly more teratogenic than carbamazepine, and that the combination of Sodium Valproate and Lamotrigine (as a polytherapy) is particularly teratogenic.

**Dr Peter Feldschreiber**<sup>52</sup>, reviewing the relevant regulatory history for this submission, notes that by November 2014, the Pharmacovigilance Risk Assessment Committee of the EMA CMDh<sup>53</sup> (**PRAC**) recognised that the published data, together with more recent studies, showed that 30 – 40% of children exposed to Sodium Valproate in the womb had developmental problems, including delayed walking and talking, memory problems, difficulties

<sup>50</sup> Morrow et al., 2005: Malformation Risks of Anti-epileptic drugs in pregnancy:  
<http://www.cardiffandvaleuhb.wales.nhs.uk/sitesplus/documents/1143/MalformationRisks%20of%20AEDs.pdf>

<sup>51</sup> <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1528-1167.2005.00323.x>

<sup>52</sup> See [Appendix G](#) for further information regarding Dr Peter Feldschreiber.

<sup>53</sup> CMDh Coordination group for mutual recognition and decentralised procedures human  
<http://www.hma.eu/cmdh.html>

with speech and language and lower intellectual ability. There was also evidence of increased risk of autism, and a suggestion that such children were more likely to develop attention hyperactivity disorder.

As a result the CMDh endorsed new recommendations that ‘on package’ warnings should be strengthened regarding the teratogenic potential of Sodium Valproate and that prescribing practices should be tightened to ensure that the drug was only prescribed in pregnancy when full and frank information had been provided directly to the patient; and only in circumstances where there were no alternative medications *are* suitable for the patient.<sup>54</sup> This set of PRAC recommendations in 2014 prompted renewed efforts in the UK to better regulate the prescription of Sodium Valproate.

Dr Feldschreiber’s complete review of the Pharmacovigilance issues relevant to this submission is provided at **Appendix F**.

### *The Sodium Valproate Toolkit*

During 2015 the MHRA (in consultation with clinicians and patient support groups, collectively known as the Valproate Stakeholders Network (VSN) developed the Sodium Valproate Toolkit<sup>55</sup>, in order to ensure female patients were better informed about the risks of taking Sodium Valproate medicines during pregnancy, this toolkit comprised:

- A checklist for clinicians
- A patient card for pharmacists to give to patients
- A patient brochure
- A brochure for health care professionals

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[http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/referrals/Valproate\\_and\\_related\\_substances/human\\_referral\\_prac\\_000032.jsp%26mid%3DWC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp%26mid%3DWC0b01ac05805c516f)

<sup>55</sup> <https://www.gov.uk/Government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients>

- Patient Information Leaflets
- A template letter inviting all patients prescribed Sodium Valproate preparations to attend a clinical review with their GP
- Updates to all GP prescribing software displaying warnings each time a VPA script is written: and
- A written warning on the outside of the Epilim box

Yet, despite the publication of the MHRA Valproate Toolkit in February 2016, there appears to have been a continued failure to ensure that key information, now better packaged and clearer than ever before, actually reached those for whom it had been specifically designed.

This failure is exposed by three publications in particular:

- A survey of women in **April 2016** found that of those taking valproate (n=624), 20% were not aware of any of the risks of valproate in pregnancy and <20% had received any of the educational materials newly created by the MHRA<sup>56</sup>.
- This survey was repeated in **2017**, when it was found that 18% of women taking the epilepsy medicine sodium valproate didn't know the risks this medicine can pose during pregnancy and 28% of women said that they had not been informed of the risks of this medicine in pregnancy<sup>57</sup>.
- Further, a National Reporting and Learning System (NRLS) search, for incidents involving valproate reported **since January 2015**, identified 13 reports that indicated valproate had been prescribed to pregnant women, including two reports that specifically identified that no discussion of the risks in pregnancy had occurred.

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<sup>56</sup> [Ref.12] [https://improvement.nhs.uk/uploads/documents/Patient\\_Safety\\_Alert\\_-\\_Resources\\_to\\_support\\_safe\\_use\\_of\\_valproate.pdf](https://improvement.nhs.uk/uploads/documents/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf)

<sup>57</sup> <https://www.epilepsy.org.uk/news/news/almost-one-fifth-women-taking-sodium-valproate-epilepsy-still-not-aware-risks-pregnancy>

For example: *“Patient ... on valproate. No discussion in notes about information or risks given to young female patient taking valproate.”*<sup>58</sup> *Greater interoperability is needed between the NRLS and the MHRA Yellow Card.*

Campaigners report that whilst the MHRA 2016 Toolkit was comprehensive, and there is some evidence of reduced prescription of Sodium Valproate for the relevant period, the reduction in prescriptions is not as significant as had been hoped.

Clearly, further regulatory action was needed: In **April 2017**, the MHRA issued a further **Patient Safety Alert**<sup>59</sup> requiring all GPs and community pharmacies to ensure that key information was communicated systematically and directly to users of Sodium Valproate: Urgent action points included:

- Develop an action plan to ensure that all women and girls of child bearing age prescribed Sodium Valproate are systematically identified to ensure that relevant information and resources can be targeted.
- Ensuring all relevant resources are embedded in local practices: and
- Ensure that all staff are aware of the risks and relevant MHRA resources

In **February 2018**, the EMA issued updated recommendations concerning the prescription and regulation of Sodium Valproate in all Member States. Once again these recommendations were prompted, at least in part, by the submissions of campaigners including groups such as OACS Charity and FACSaware.

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[https://improvement.nhs.uk/uploads/documents/Patient\\_Safety\\_Alert\\_-\\_Resources\\_to\\_support\\_safe\\_use\\_of\\_valproate.pdf](https://improvement.nhs.uk/uploads/documents/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf)

59 [https://improvement.nhs.uk/uploads/documents/Patient\\_Safety\\_Alert\\_-\\_Resources\\_to\\_support\\_safe\\_use\\_of\\_valproate.pdf](https://improvement.nhs.uk/uploads/documents/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf)

This latest set of recommendations now published by the EMA states as follows<sup>60</sup>:

- In pregnancy - valproate must **not** be used. However it is recognised that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.
- In female patients from the time they become able to have children – valproate must not be used unless the conditions of the new pregnancy prevention programme are met.
- The PRAC has also recommended that the outer packaging of all valproate medicines must include a visual warning about the risks in pregnancy. In addition to boxed text, this may include a symbol/pictogram, with the details to be adapted at national level.
- A patient reminder card will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.
- Companies that market valproate should also provide updated educational materials in the form of guides for healthcare professionals and patients.
- In addition, EMA have recommended that Member States implement a pregnancy prevention program for those using Sodium Valproate: That program includes:
  - Assessing patients for the potential of becoming pregnant, and involving the patient in evaluating her individual circumstances and supporting informed decision making,
  - pregnancy tests before starting and during treatment as needed,
  - counselling patients about the risks of valproate treatment,
  - explaining the need for effective contraception throughout treatment,
  - carrying out reviews of treatment by a specialist at least annually,
  - introduction of a new risk acknowledgement form that patients and prescribers will go through at each such review to confirm that appropriate advice has been given and understood

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[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate\\_and\\_related\\_substances/human\\_referral\\_prac\\_000066.jsp&mid=WC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000066.jsp&mid=WC0b01ac05805c516f)

It is anticipated that the changes now recommended by the EMA, will be implemented in the UK by the MHRA over the next year. A formal announcement by the MHRA is due on 24 April 2018.

However, campaigners remain concerned regarding:

- **The use of polytherapy:** There is still much confusion among GPs and neurologists regarding what is safe to do when a woman presents as pregnant while on Sodium Valproate: Published data shows polytherapy poses a greater risk, but it is feared that too frequently women are being changed onto a new additional medication while they are pregnant, which poses a greater risk than staying on Sodium Valproate alone.
- **Lack of NICE Engagement:** The slow pace at which NICE have responded in issuing guidelines on how to transfer a patient from one AED to another; and
- **Importance of Joined up Care:** That the multi-disciplinary nature of providing comprehensive and appropriate pregnancy advice to epileptic women (ideally involving neurologists, GPs and other specialists working together), means that the ideal of joined up advice and health care envisaged by the updated guidance may be much more difficult to achieve in practice.

Campaigners note that some of these challenges have been recognised by professional bodies and discussions are taking place regarding provision of information and support through Shared Care Agreements. However, more clarity is required around who is responsible for what within this dissemination process. Health, Education and Social Care providers need to work together to develop resources about Alternative Parenting Options. Campaigners note that at no point have any agencies sought to provide women with a positive alternative to becoming pregnant in order to experience parenting.

In our submission, all of the full and frank information provided directly to patients and all of the practices aimed at embedding awareness of the adverse risks associated with Sodium Valproate within the clinical community introduced since 2014, could have been introduced by the regulator/manufacturer significantly earlier, at least as early as 2003 to coincide with the preparation of the NICE guidelines but on a precautionary basis to enable competent clinical

decision-making, from at least as early as 1996. This precautionary approach to regulation must be improved and maintained as we move into post Brexit reality.

## **Section 4: Failure of the Regulator and Manufacturer to Safeguard the Patient**

As set out in **Section 2** under the terms of the Medicines Regulation Act 1968 and subsequent legislation, the MHRA and its predecessors, were under a statutory duty to safeguard patients through ensuring appropriate disclosure from the manufacturer and accurate labelling of medicines for the benefit of the patient.

In our submission, despite being in possession of extensive information regarding the teratogenic potential of Sodium Valproate the manufacturer and the regulator made the decision not to communicate that information to the clinician in full, or to the patient at all, until at least 30 years after the date of first licensing Epilim for the UK market.

Dr Peter Feldschreiber<sup>61</sup>, in reviewing the history of FVS for this submission, has concluded that:

*'It is difficult to understand why the manufacturers and the regulators delayed in recognising the public health need for warnings regarding these potentially devastating clinical teratogenic adverse events....*

*...The regulatory authorities (MHRA and EMA) had a duty to ensure the studies were properly evaluated to determine whether an appropriate benefit risk had been assured*

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<sup>61</sup> A short biography re Dr Peter Feldschreiber is provided at **Appendix G**. Dr Feldschreiber's full account is provided in **Appendix E**.

## *Failure to warn*

The recent publication of confidential minutes from the CSM appears to indicate that since at least as early as 1974, the incumbent Government and regulatory authority, knew much more about the teratogenic potential of Sodium Valproate than was communicated to users of the medication.

In our submission, evidence is now available showing that in 1973-74 the CSM, in consultation with the manufacturer, made the decision to omit key information from the packaging inserts of Sodium Valproate medications in order to ensure that *'there would be no danger at all of patients themselves seeing it'*, and suffering the *"fruitless anxiety"* triggered by knowledge of the teratogenic risks associated with Sodium Valproate<sup>62</sup>.

Yet, in our submission, the regulatory failures that have defined the prescription of Sodium Valproate within the UK market are not confined to decisions made in the 1970s. As set out below, inadequate information and/or mechanisms to distribute that information, was provided by the manufacturer/regulator until as recently as 2014.

In our opinion, based upon detailed analysis, the Manufacturer and Regulator until at least 2005, failed to provide adequate information directly to patients regarding the teratogenic risks of Sodium Valproate. We note the following in particular:

- Before 1997 there was no reference in the Patient Information leaflet (PIL) as to the nature and magnitude of the risk of damage to the foetus from the known teratogenic nature of Sodium Valproate.
- Until 2003 PILs were positively misleading in that they did not spell out the increased risk of congenital abnormalities to pregnant women with epilepsy who took Epilim, but rather suggested this was a risk shared by all pregnant women with epilepsy whether exposed to SV, other AEDS, or none at all.

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<sup>62</sup> [The authors of this submission do not currently have access to this material, however, it is submitted that the existence of this material is now beyond doubt] - <https://www.theguardian.com/society/2017/sep/26/sodium-valproate-birth-defect-risks-known-40-years-ago-campaigners>.

- Even today, charity leaflets printed in 2013 are still available in Neurology Out Patient Clinics; these leaflets do not spell out the known risks associated with Sodium Valproate and do not reflect the latest MHRA guidance<sup>63</sup>.

### *Failure to warn clinicians*

It is clear, in our view that more extensive information was provided to clinicians by the Manufacturer and Regulator, than to patients. Additional information was provided to clinicians in the form of 'Datasheets' and 'Specific Product Characteristic' information. However, in our opinion, there were nevertheless significant omissions in the information provided to clinicians over time. We note the following in particular:

- Until **1985** clinicians were not expressly advised to monitor the pregnancies of women prescribed Sodium Valproate.
- Until **1994** clinicians were not advised to ensure the prescription of Sodium Valproate as a monotherapy for women of childbearing age, or for pregnant women who were already using Sodium Valproate at the date of conception.
- Until **1995** clinicians were not advised that the lowest effective dosage of Sodium Valproate should be used for female users during pregnancy.
- Until **1995** clinicians were not advised to inform female users of the risks/benefits associated with Sodium Valproate using during pregnancy.
- Until **1997** clinicians were not advised to avoid use of Sodium Valproate except in cases where patients were resistant to all other available AEDs.
- Until **2003** clinicians were not advised that Epilim increased the risk of congenital abnormality in excess of the risks associated with other Sodium Valproate preparations or the risks associated with epilepsy generally.
- Until **2010** clinicians were not advised to ensure that female patients were consulted about the known risks of in utero exposure to Sodium Valproate prior to first prescription of Epilim and to ensure that adequate counselling was provided to patients.

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<sup>63</sup> Epilepsy Society Leaflet, dated August 2013 which was recently found by a campaigner at her out patient clinic.

- Until **2017** the regulator/manufacturer took inadequate steps to ensure that full and frank information was provided to clinicians with clear instructions to embed appropriate patient reviews and counselling into local practice.

In our submission, these failures significantly limited the scope for individual clinicians to act as '**Learned Intermediaries**' between the Manufacturer/Regulator and the individual Patient. As such the responsibility for such failures to warn is attributable directly to the Manufacturer and Regulator.

## **Section 5: The Responsibility of the Medical Profession**

It is of course appropriate, to investigate the role of GPs and other health practitioners in any failure to fully communicate the adverse health effects and risks associated with a medicine or medical device, directly to the patient. However, as noted above, this responsibility can only extend to information provided to clinicians by the Manufacturer/Regulator in relation to any product.

As set out above, in our opinion, publication of the 2005 NICE guidelines arguably provided all clinicians with far clearer guidance in relation to the importance of pre-conception counselling and avoiding Sodium Valproate prescription to women with epilepsy wherever possible, or, if unavoidable, minimizing dosage and avoiding polytherapy.

However, in our opinion, prior to 2005, a review of the relevant documentation suggests that clinicians did not have sufficient information to act as Learned Intermediaries between the Manufacturer/Regulator and the Patient and as such any legal liability in relation to FVS cannot, and should not, be attached to individual clinicians (save in the most egregious circumstances), particularly where the Manufacturer/Regulator are not also joined as Defendants.

This, in our submission, is consistent with the 'strict liability regime' imposed by the relevant legislation, the Product Liability Directive/Consumer Protection Act 1987, which was intended to ensure that the Manufacturer of a drug/device, and the incumbent Regulator, cannot simply

absolve itself of potential civil liability by pointing the finger of blame at individual clinical practitioners.

In this context, it is important that the Review has in mind the relatively recent Supreme Court decision of *Montgomery v Lanarkshire Health Board*<sup>64</sup>.

This landmark decision changed the law on informed consent with significant ramifications for practicing doctors. Prior to 2015 the test was whether a reasonable body of medical practitioners practicing in the same discipline would have acted in the same way (the Bolam/Bolitho basis). The test is now one of materiality in the context of a reasonable patient. Namely, whether in the individual circumstances “*a reasonable person in the patient’s position would likely attach significance to the risk*”<sup>65</sup> or whether the doctor should be, or is, aware that the particular patient would see the risk as significant<sup>66</sup>.

Since that decision the Courts have allowed amendments to pleaded cases to include consent based arguments that were not included at the time that proceedings were issued, some of which have been successful<sup>67</sup>. It is poignant to note that one of those cases, *S v Smith* that came before the High Court in November 2017, was issued against a neurologist for insufficient warning of the risks of developmental delay to a child exposed to Sodium Valproate pre-natally<sup>68</sup>. The case was settled confidentially.

As such *Montgomery* creates the potential for extensive litigation against individual practitioners in relation to Sodium Valproate prescription, with the NHS potentially left to pick up the Defendant bill.

In our submission that is neither desirable for the NHS nor is it legally or morally just for the Manufacturer to avoid contributing to any compensation paid in relation to FVS at the continued expense of the NHS/taxpayer.

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<sup>64</sup> *Montgomery v Lanarkshire Health Board* [2015] 1 AC 1430] found here: [http://www.bailii.org/cgi-bin/format.cgi?doc=/uk/cases/UKSC/2015/11.html&query=\(Montgomery\)+AND+\(V\)+AND+\(Lanarkshire\)](http://www.bailii.org/cgi-bin/format.cgi?doc=/uk/cases/UKSC/2015/11.html&query=(Montgomery)+AND+(V)+AND+(Lanarkshire))

<sup>65</sup> Ibid, paragraph 65 – 73

<sup>66</sup> Ibid, paragraph 72

<sup>67</sup> <http://www.bmj.com/content/357/bmj.j2224>

<sup>68</sup> *S v Smith* QBD (2016-2017)

*Were the regulatory failures in relation to Sodium Valproate simply 'of their time'?*

In responding to reports concerning the withholding of information from patients in 1973 a spokesperson for the MHRA has stated as follows:

*"At that time, it would have been for the doctor to decide how much information a patient was given about their medicine.*

*"This attitude to provision of information to patients would not have been unusual at that time, particularly in relation to lifesaving medicines such as anticonvulsants, as there was a concern that information about side effects may have caused people to stop treatment<sup>69</sup>."*

In our submission that response is wholly inappropriate and legally inaccurate for the following reasons:

- It is based upon a mischaracterisation of the **regulatory** regime in 1973, which as set out in **Section 2** required manufacturers and regulators to ensure that medicines were labelled in such a way as to ensure the safety of all licensed products. Failing to advise patients directly of the teratogenic risk of a medication directly jeopardised the safety of the unborn children;
- It fails to acknowledge that, as set out above, the failure to disclose and communicate key information to clinicians and patients regarding Sodium Valproate is not a relic of the 1970s but has been ongoing in relation to Sodium Valproate from 1973 until at least as recently as 2005. Whilst it is acknowledged that the duty to warn recognised by the House of Lords in ***Sidaway v Board of Governors of the Bethlem Royal Hospital and the Maudsley Hospital*** (1984) QB493 emphasised the primacy of the body of responsible medical opinion as the test of competence in warning, the failure

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<sup>69</sup> <https://news.sky.com/story/valproate-risk-hidden-from-pregnant-women-for-decades-11053919>

to equip **clinicians** with sufficient information with which to warn, undermined their ability properly to warn patients of the full scale of risks involved with Valproate treatment during pregnancy at least until 2003. That warning obligation has now been considerably enhanced by **Montgomery and Lanarkshire Health Board**.

- It fails to acknowledge that until 2018 there have been inadequate efforts to embed procedure and education within clinical practices in order to ensure that full, frank and appropriate information was provided to patients.
- It fails to take full account of the historical context within which the UK medicines regulations were first developed, namely the Thalidomide scandal, which resulted from the release on to the UK market of a known teratogen with inadequate labelling and information for patients and clinicians and the strict liability objectives intended by the European Product Liability Directive: EEC374/85.
- It also fails to take account of the fact that the controversy surrounding Sodium Valproate in the UK is not an isolated incident of regulatory failure, but rather, forms part of a chain of medical product regulatory failures, concerning both medicines and medical devices, over the past thirty years. From Thalidomide onwards through to the recent metal-on-metal hips scandal there have been a series of other failures which include; Primodos, Vioxx, Seroxat, Human Growth Hormone (iatrogenic CJD) and more recently Vaginal Mesh and PIP breast implants.
- It further fails to take into account the fact that regulatory failings were specifically identified in a House of Commons Report dated **2005**, '*Influence of Industry on the MHRA*'<sup>70</sup> in which the shortcomings of the UK medicines regulatory regime were identified: For example:
  - .....'*Our inquiry revealed major failings in the regulatory system*'.
  - ... '*We have concerns about the licensing process, including the evaluation of clinical trials; the control of marketing; staffing levels, particularly in relation to post-marketing evaluation; the withdrawal of drugs; the Yellow Card system; and licensing related to generics*'.
  - .....'*We recommend that the MHRA publishes, in some form of useable database, the material it receives from drug companies and the assessments it sends to advisory bodies at the time it sends them. The MHRA does not*

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<sup>70</sup> House of Commons, Health Committee Report 2004-2005 '*The Influence of the Pharmaceutical Industry*', produced 22 March 2005

*routinely examine raw data submitted with the licence application but is dependent on summaries provided by the applicant'*

- *...'Overwhelming evidence is required by the regulator before drug warnings are proposed or when drugs may be withdrawn: Only 19 drugs have been withdrawn between 1993 and 2004. On the other hand, medicines can be licensed in the absence of adequate data or investigation into possible adverse reactions and with proof of only limited therapeutic value.'*
- *...'Post-marketing surveillance in the UK is inadequate. This has several causes: the lack of effective post-marketing investigation of drug benefits and harms in real life situations, and institutional indifference to the experience and reports of medicine users'.*

We submit that this list of failings is as true today as it was in 2005. Thirteen years on the Government has failed to act to improve medical device and pharmaceutical regulation in the UK: The Government's failure to act has had tragic consequences not only for those represented by OACS Charity and FACSaware in relation to Sodium Valproate but by placing all UK patients at risk.

## **Section 6: Failure of the Justice System**

Just as the failures of the regulator and manufacturer to inform patients about the teratogenic risks associated with Sodium Valproate were responsible for creating the legacy of FVS in the UK, so systemic failings within the UK justice system have prevented those affected by FVS from achieving justice through the Courts.

This section provides a brief overview of:

- The history of FVS/FAC litigation in the UK;
- The hurdles litigants face in the UK in holding manufacturers and regulators to account in relation to defective medicinal products;
- The current potential for FVS victims in the UK to mount a new legal action in order to seek justice and compensation.
- Successful FVS litigation in other jurisdictions.

### *The History of FVS/FAC litigation in the UK*

In the late 1990's a large number of individual Legal Aid certificates were issued to FVS Claimants who brought individual common law claims against individual clinicians who had prescribed Sodium Valproate across the UK. One or two of these cases settled but the vast majority were robustly and successfully defended on a **Bolam/Bolitho** basis.

In the light of these many failures, the Legal Services Commission supported the development of a Multi Party Action brought under the EU Product Liability Directive, its UK domestic expression, the Consumer Protection Act 1987 and the Congenital Disabilities (Civil Liability) Act 1976, against the manufacturer, Sanofi Synthelabo Ltd ('**Sanofi**'), the English subsidiary of the French multi national pharmaceutical company.

In 2004, legal proceedings were issued in the UK against Sanofi, in relation to FVS caused by in utero exposure to Epilim; the brand name of the Sodium Valproate compound marketed by Sanofi in the UK. This litigation became known as the Fetal Anti Convulsant or 'FAC Litigation'.

The claim was subject to a Group Litigation Order which consolidated the individual claims of more than 100 children across the UK all of whom had been diagnosed with FVS. Group A comprised 100 fully prepared cases ; Group B comprised 67 cases issued, served and stayed in order to protect claims which would otherwise become statute barred by the effect of the 10 year long stop.

All of those injured were children, and by application of section 6(3) of the Consumer Protection Act, the Congenital Disabilities (Civil Liability) Act 1976 was also engaged by this litigation; such that the claim was intended to consider the Defendant's liability to both the mothers involved and their children.

The Claimants argued that product information concerning warnings given in relation to the teratogenic capacity of a product is irrelevant in circumstances where the injury arises post conception. Or that if they are relevant, the warnings and other product documentation in this instance, failed to properly communicate to users the magnitude of teratogenic risks associated with Epilim, as outlined above in this submission.

In October 2010<sup>71</sup>, just three weeks before the FAC Litigation was scheduled to begin a six month listing in the High Court in London, the Legal Services Commission terminated the funding for the case. As a result, Irwin Mitchell, the solicitors representing the families involved in the FAC Litigation advised discontinuance. A confidential settlement was entered into in relation to legal costs between the families and the Defendant manufacturer: None of the children and families affected by FVS in the UK and who participated in the action received any compensation. To date, no follow-up legal action has ever been attempted in the UK.

The effects of the failure of that legal action have been far reaching at many levels, legal, financial and regulatory; however, it is important to remember that they are also immensely personal. One parent involved in the legal action told a press conference shortly after withdrawal of funding for the case:

*“We have lost our battle today and the Government is telling us that it wasn’t the drugs company’s fault. One day my daughter will grow up and ask me what happened - and I will have to tell her that it wasn’t the fault of the drugs company, it wasn’t the fault of the Government, it wasn’t the fault of the doctor and it wasn’t the fault of the neurologist. And then I will have to say that it wasn’t my fault. The only person left is her. There have been geneticists who believe certain children are more genetically disposed to having fetal valproate syndrome. Could this be true - is it her fault?”*

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<sup>71</sup> <https://www.theguardian.com/society/2010/nov/08/legal-aid-anti-epilepsy-drug>

**It was not her fault**, but she and her family continue to suffer without answers and without compensation.

### *The 'Justice Gap' for product liability Claimants in the UK*

In our submission the following factors historically and currently make it very difficult for Claimants to mount successful legal actions against manufacturers and/or regulatory bodies within the UK:

- **Inequality of 'arms'**: There is an inherent imbalance of resources between patients and pharmaceutical/medical device companies in any litigation: Individual litigants even when grouped together via Group Litigation Orders are a poor match for multinational corporations with very deep pockets. The very real risk of losing a case and having to pay (even some part) of the costs incurred in product liability litigation is a powerful deterrent to even the boldest Claimants and their lawyers. Hence the attraction of the discontinuance in the Fetal Anti Convulsant Litigation that avoided any question of enforcement of the Defendant's costs. Unavoidably, from a Manufacturer's viewpoint the impact of a successful claim anywhere in the world can be catastrophic, not only for that product in that market but also to the overall manufacturing brand. Unsurprisingly, therefore these claims are robustly defended at whatever (tax-deductible) cost. Courts hesitate to give equal weight to these immense brand values on the one hand and the impact of injury on individual lives and on the lives of families.
- **Complex expensive litigation**: Product liability cases are notoriously 'expert heavy', the technical and scientific information that the Claimants must accumulate in order to even investigate a claim against a manufacturer make any such action very expensive from the outset. By contrast, not only will the manufacturer have much deeper pockets it will also have at its disposal an established body of scientific and technical experts who it employs and who are already immersed in the development of the product. Furthermore it can readily call upon a wider cohort of independent experts whose research it funds from its R&D budget.
- **Lack of established case law**: The difficulty for claimants in taking a claim against a manufacturer to trial in the UK, let alone winning it, is evidenced by the lack of

established case law in this area: In turn, the lack of established precedent makes this area of law more opaque and so more difficult for claimants and their insurers to properly evaluate the risks associated with product liability litigation in the UK. This has the effect of discouraging legal actions against manufacturers. Indeed, it was not until 2000 that an extensive judicial examination of the meaning of 'defect' took place in the UK in **A v National Blood Authority**. At the date of writing another substantive judgment is anticipated in the Pinnacle Metal on Metal Hip Litigation, but it has taken 18 years before another group of claimants could take a manufacturer through the UK courts. In turn, this caution in identifying the Manufacturer as the Defendant may compel litigants to attempt litigation against clinicians which puts further pressure on NHS resources. The decision in **Montgomery v. Lanarkshire** may only redouble this effect whilst litigation against Manufacturers remains such an expensive and unknown prospect.

#### *Relevant Legislation: The CPA and the PLD*

Marcus Pilgerstorfer,<sup>72</sup> has provided us with an independent assessment of the current legal position under the relevant legislation, the Product Liability Directive and the Consumer Protection Act 1987. His analysis is set out in full at **Appendix F**.

In summary, the current legislative framework within which a Claimant may bring an action against a manufacturer in the UK on the basis of a defective product, is under-developed as a result of a lack of consistent case law. The definition of 'defect' under the legislation is still in flux, and the case law that has emerged across Europe is, as per Mr Pilgerstorfer's summary, Janus-faced in terms of establishing what the Claimant must prove in order to prove defect on the 'balance of probabilities'. Consequently, potential Claimants, their lawyers, and their insurers are discouraged from bringing substantive actions against manufacturers in the UK such that Claimants suffer from a lack of access to justice and consumers in general suffer from a lack of accountability on the part of the manufacturer.

#### *View from Europe*

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<sup>72</sup> Ashort biography for Marcus Pilgerstorfer appears at **Appendix G**.

Duncan Fairgrieve<sup>73</sup>, has provided a summary of recent developments in Europe which are of relevance to liability in the pharmaceutical sphere in general and Epilim in particular. An edited version of Dr Fairgrieve's comments are provided below.

As part of the formal review process under the Directive,<sup>74</sup> the European Commission launched an evaluation of the Product Liability Directive in 2017, which was designed to examine the key features of the Directive -defect, product, defences etc-, to determine whether the Directive was "*still fit for purpose.*"

A series of initiatives were put in place as part of that formal evaluation, including an external study by Ernst & Young, and public consultation in order to collect stakeholders' feedback on the application and performance of the Directive. The Ernst & Young study has not yet been officially published but would seem to indicate that the number of product liability claims have increased over past few years, with a significant number of claims brought to court across the EU,<sup>75</sup> with an aggregate rate of success of 60%, but illustrates that there remain difficulties of injured parties in obtaining compensation (e.g. proof of the defect or the causal link between defect and damage).

In terms of the public consultation, the European Commission received 113 responses with 35% of responses from producers, 35% from consumers, as well as of course from others (e.g. from the public sector and civil society).<sup>76</sup> As to the results of that survey, the standout figure is that 68% of respondents stated that they believed the Directive strikes a fair balance between the interests of producers and those of consumers. As in previous reports, the indication is that for a majority of stakeholders, the right balance has thus been found in global terms. That stark statistic however conceals the extent of concerns about the operation of the

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<sup>73</sup> A short biography re Dr Fairgrieve is provided at **Appendix G**.

<sup>74</sup> It is provided in Article 21 of the Directive that the Commission must prepare a report to the Council on the application of the Directive on a five-yearly basis. This has given rise to a series of Commission reports since the inception of the Directive in 1985, with the 5th Review currently underway.

<sup>75</sup> Almost 800 between 2000- 2016 : *Minutes of Product Liability Conference, Brussels 20 October 2017*, (European Commission, Brussels, 30 Nov 2017, Grow.ddg1.b.1/VS/sv(2017) 6611689). This figure seems surprisingly low given the large number of claims in jurisdictions such as France and Austria.

<sup>76</sup> European Commission, Brief Factual Summary on the Results of the Public Consultation on the Rules on Producer Liability for Damage Caused by a Defective Product (Brussels, 30 May 2017).

Directive in certain specific spheres. Such appears to be the case in respect of the application of the current rules to new technology, with only half of producers and consumers thinking that the Directive was adequate to cover needs relating to new technology.<sup>77</sup>

Concerns have similarly been expressed about the operation of the Directive in respect of injury caused by pharmaceutical products. A variety of such issues have been raised, and discussion at the recent European Commission-organised Product Liability Conference on this very topic is particularly instructive.<sup>78</sup> The representatives of *AMALYSTE* (*French Association of Stevens-Johnson Syndrome Victims*), *APESAC* (*French Association of Victims of Valproate*) and *Les Filles DES Association* (*French Distilben victims*), speaking on behalf of the *French Collective of Victims of Medicines*, voiced a number of concerns about the operation of the Directive in respect of injuries caused by medicines, including the difficulty of proving defect and the effects of the various limitation periods, in particular the 10-year long stop cut-off period for claims.<sup>79</sup> The point was also made that the “*inadequacy of the Directive*” had resulted in “*some countries [setting] up dedicated compensation funds.*” It was recorded also that the President of the French victims’ support group of Dépakine / Epilim (APESAC) had “*explained that it was necessary to create a compensation fund for victims of valproate in France in order to circumvent the problem of the 10-year limitation in the directive. These funds are, however, limited to certain drugs, corresponding with the media pressure they trigger and the responsibility of the authorities themselves.*” UK practitioners added their voice to such a sentiment: UK law firm Hugh James challenged the perception of the success of the Directive. In England and Wales a fault-based scheme produces a success rate in excess of 80%, but for the Product Liability Directive with no fault, it is only 60%. The Firm pointed out that the statute of limitation, specifically the ten-year provision, is not working in the case of

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<sup>77</sup> A significant number of respondents considered that the application of the Directive might be problematic or uncertain for some such products, such as products performing automated tasks based on algorithms, data analytics, self-learning algorithms or products purchased as a bundle with related services.

<sup>78</sup> *Minutes of Product Liability Conference, Brussels 20 October 2017*, (European Commission, Brussels, 30 Nov 2017, Grow.ddg1.b.1/VS/sv(2017) 6611689).

<sup>79</sup> *Minutes of Product Liability Conference, Brussels 20 October 2017*, (European Commission, Brussels, 30 Nov 2017, Grow.ddg1.b.1/VS/sv(2017) 6611689), page 3.

medicines, and that it is particularly unfair in cases that involve children.<sup>80</sup> Similar sentiments were voiced from other participants at the meeting.<sup>81</sup>

On the face of it therefore prospects for successful litigation in England & Wales might seem better than they were in 2010 when the first FAC Litigation foundered; however, for the reasons set out below for the vast majority of FVS victims litigation is very unlikely to be a successful route to compensation.

## Section 7: Prospects for new legal action by FVS victims in the UK

The following factors have renewed campaigners' interests in the prospect of litigation against the manufacturer and UK regulator:

- Firstly, **new authoritative epidemiological information** now demonstrates that the increased risk of congenital injury as a result of in vitro exposure to Sodium Valproate is significantly higher than the background rate in the UK epileptic population and/or significantly higher than the rate of abnormality associated with in utero exposure to other, in most cases, alternative Sodium Valproate preparations. **Veroniki 2017** performed a systematic review and meta-analysis across 29 studies with 5100 children, comparing the outcomes for those children born to mothers using Sodium Valproate amongst other AEDs during pregnancy. In 11 of the cohort studies reviewed, Sodium Valproate, amongst all AEDs, was the only medication that had a statistically significant association with development delays, autism and psychomotor delay<sup>82</sup>.
- Secondly, The Epilim / Depakine saga became a major health scandal in France, and the French Government instructed in 2015 the public healthcare watchdog, the *Inspection Générale des Affaires Sociales* to undertake an investigation into this matter. This resulted in the publication of a report in February 2016 entitled "*Enquête*

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<sup>80</sup> Ibid, page 4.

<sup>81</sup> "The *Bulgarian Ministry of Economy* agreed that the area of medicines should be revised, but pointed out that this issue is not new and that it was already assessed at the time of the adoption of the Product Liability Directive." (ibid page 4)

<sup>82</sup> Veroniki et al 2017, Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding, *BMJ Open*

*relative aux spécialités pharmaceutiques contenant du valporate de sodium.*<sup>83</sup> The report concluded *inter alia* that there had been “*inertia*” on the part of the French and European health authorities as well as Pharma companies in respect of the relevant information provided to doctors & patients (see page 69).

- As a consequence, the French Government announced during summer 2016 the setting up of a statutory fund to compensate victims.<sup>84</sup> The Fund has now been created by means of a legislative amendment passed in November 2016 of the Public Health Code (*Code de la Santé Publique*),<sup>85</sup> with a mechanism based around a pre-existing public body, the Oniam (*Office National d’Indemnisation des Accidents Médicaux*).
- In parallel, legal proceedings have been brought against the manufacturer of Epilim / Depakine. The main victims’ support group in France, APESAC, launched in May 2017 a group action<sup>86</sup> under the auspices of the new French group action procedure applying to healthcare products.<sup>87</sup> Details of the proceedings featured in the French media in December 2016,<sup>88</sup> and various procedural hearings have been held before the courts since then. Unitary civil claims have also been brought by those affected. One of these gave rise to a successful claim, upheld by the Orléans Court of Appeal on 20 November 2017.<sup>89</sup>
- Over and above this, criminal proceedings have also been launched in France for alleged “aggravated misleading information and involuntary personal injury (“*tromperie aggravé et blessures involontaires*”) arising from the commercialisation of Depakine during the period of 1990 – 2015.
- Furthermore on 20 November 2017<sup>90</sup>, in a case brought on behalf of a single claimant injured as a result of her in utero exposure to Depakine, **the French Court of Appeal**

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<sup>83</sup> [www.igas.gouv.fr/IMG/pdf/2015-094R.pdf](http://www.igas.gouv.fr/IMG/pdf/2015-094R.pdf)

<sup>84</sup> See [http://social-sante.gouv.fr/IMG/pdf/16\\_24\\_08\\_-\\_cp\\_acide\\_valproique\\_-\\_mise\\_en\\_place\\_d\\_un\\_fonds\\_d\\_indemnisation.pdf](http://social-sante.gouv.fr/IMG/pdf/16_24_08_-_cp_acide_valproique_-_mise_en_place_d_un_fonds_d_indemnisation.pdf)

<sup>85</sup> Articles 1142-24-9 à L. 1142-24-18 of the *Code de la Santé Publique*.

<sup>86</sup> See M-J. Azar-Baud, « Variations autour du Régime de l’Action de Groupe » in *Semaine Juridique Entreprise et Affaires*, n° 27, 6 Juillet 2017, 1380.

<sup>87</sup> See Articles L. 1143-1 à L. 1143-22 of the *Code de la Santé Publique*.

<sup>88</sup> [http://www.lemonde.fr/sante/article/2016/12/13/la-depakine-cible-de-la-premiere-action-de-groupe-en-matiere-de-sante\\_5048007\\_1651302.html](http://www.lemonde.fr/sante/article/2016/12/13/la-depakine-cible-de-la-premiere-action-de-groupe-en-matiere-de-sante_5048007_1651302.html)

<sup>89</sup> Orléans Court of Appeal, N° 16/00141.

<sup>90</sup>

[http://www.liberation.fr/france/2017/12/11/depakine-sanofi-condamne-pour-la-premiere-fois\\_1615859](http://www.liberation.fr/france/2017/12/11/depakine-sanofi-condamne-pour-la-premiere-fois_1615859)

**found in favour of the Claimant** [No: 496/2017 – No RG: 16/00141: SA Sanofi v Ms Carrera]: The Court determined that Depakine **is “a product that did not offer the safety of which we can legitimately expect” (highlight this statement)** and found Sanofi liable under the Product Liability Directive. The Court did not accept Sanofi’s argument that sufficient warnings about the teratogenic capacity of Depakine had been provided to users through product information leaflets and other product documentation. The claimant’s doctors had mentioned to the patient a minor risk of cleft lip or heart deformity as a result of Depakine use in utero. The patient was assured that if she took Speciafoldine, the teratogenic effects of the Depakine would disappear. However the patient leaflet did not identify the teratogenic risk among the possible adverse effects of the product as taken by a pregnant woman. Sanofi have been ordered to pay a total of 3 million EUROS to the claimant and her family by way of compensation. It is understood that Sanofi are filing an appeal at the Court of Cassation, but it is also anticipated that further follow-on, potentially group, legal actions will now be issued by other Claimants within France.

It is noteworthy that the litigant in this recent action against Sanofi in France was successful in bringing a claim that would have striking similarities with any action mounted by UK FVS victims: In particular, proceedings would be issued against Defendants in the same group of companies; in relation to the same medication (albeit with a different brand name used in France – Depakine vs Epilim), under exactly the same legislation i.e. the French domestic expression of the Product Liability Directive.

On that basis, with the fact of robust epidemiological evidence showing a doubling of risk for those injured by FVS, the prospects for potential renewed litigation in the UK would appear to be very good.

However, it must also be understood that potential FVS litigants in the UK, particularly those involved with the original FAC litigation, would still face probable insuperable difficulties in seeking to mount renewed legal action in the UK, because:

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- **Time Limits under the Consumer Protection Act 1987:**

- Claims under the CPA are governed by a 3 year limitation period under section 11A of the Limitation Act 1980 which relates specifically to product liability.
- Additionally section 11A(3) of the Limitation Act 1980 imposes a 10 year long stop date, which prevents a litigant from bringing an action against the manufacturer more than 10 years after the product was put into circulation.
- As a result, it is likely that for the majority of FVS victims, and especially those over 10 years old, it is very likely that their cases will be time-barred from proceeding under the CPA.
- This will mean that many of the original litigants who were prevented from bringing their legal action by the decision of the Legal Services Commission to withdraw funding will still be unable to seek justice despite the additional epidemiological evidence now available and the recent successful French precedent<sup>91</sup>.
- It is of course possible that a potential FVS litigant would seek to issue proceedings on the basis of common law negligence rather than under CPA, thereby attempting to sidestep the 10 year long stop date imposed by section 11(A)(3) of the Limitation Act and seek to qualify for the 'exceptional circumstances' that enable litigation to be brought outside of the normal 3 year period for personal injury. However, in doing so a Claimant would also forego the 'strict liability' regime imposed upon the Defendant by the CPA and would instead need to establish fault on the basis of common law negligence. That may be possible on the facts in this case, but would likely be a costly and risky battle to fight and as such obtaining insurance for such a claim would be problematic.
- Moreover, any attempt to achieve justice and compensation for those affected by FVS by reviving historic litigation, or commencing new litigation, would necessarily involve a further delay probably three years minimum to prepare in

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<sup>91</sup> In reviewing a recent French decision under the PLD, concerning injuries suffered following provision of a anti-Haemophilus influenza Type B vaccine, the ECJ indicated that the National Courts should use some discretion in permitting the substitution of a defendant outside the 10 year long stop period. However, this related to a case in which proceedings had been issued against the wrong defendant and so offer little hope of application for the original FAC litigants.

achieving the desired outcome for a group of campaigners and victims who have surely waited long enough.

- **The fact of the discontinuation of the original 2010 claim:**
  - Unfortunately, the Claimants whose Legal Aid funding was withdrawn and whose claims had to be discontinued in 2010 would be very unlikely to be able to persuade a Court in 2018 to set aside those discontinuances.
  - Once a discontinuance is served a claim is considered to have been irretrievably ended and setting aside a discontinuance without the consent of the Defendant discontinued against is extremely difficult, even where new and favourable evidence has emerged. Reviving a Multi Party Action in this way has never been successful.

## Section 8: Other Jurisdictions

Potential FVS litigants in other jurisdictions outside of the UK have ~~fares~~ fared better than their UK counterparts. For example:

- **In France:** As set out above, Case No: 496/2017 – No RG: 16/00141
- **In the US:** Two legal claims have progressed to trial for the drug Depakote (American brand name for Sodium Valproate) against Abbot Laboratories:
  - June 2015 – successful claim against Abbott<sup>92</sup>. A jury awarded \$23 million in punitive damages in addition to the \$15 million previously awarded to a 12-year-old girl, finding that the manufacturer did not do enough to warn doctors about birth defect risks. The Claimant suffered from Spina Bifida and learning difficulties as a result of her mother using Sodium Valproate based Depakote during pregnancy. The Jury held that Abbott Laboratories should have warned doctors to try all other forms of antiepileptic drugs before prescribing Depakote to the Claimant's mother.
  - In February 2017, a jury in Ohio found in favour of Abbott Laboratories and did not award damages to a boy who was born with microcephaly (abnormally small skull) and intellectual disabilities after being exposed to Depakote in the

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<sup>92</sup> Schmidt v. Abbott, CA No. 1222-CC-0247901, Missouri Circuit Court (St. Louis).

womb. Legal claims for developmental delays have proven to not be successful in the USA as the manufacturer warned the FDA in 2005 about this risk but the regulator failed to act to warn until 2009.

## Section 9: The Legal case for a Public Inquiry

**Sections 4 and 6** above identify the failings of the regulatory and legal system in both protecting those affected by FVS and then in providing them with access to justice.

The regulatory failings and the ‘access to justice’ issues exposed by the history of FVS litigation are characteristic of the way in which patients and consumers in the UK have become disenfranchised by the current regulatory and legal systems.

In the words of the mother of a child diagnosed with FVS:<sup>93</sup>

*‘...these children and families have been let down not just by Sanofi but by the Government, by the system, by the NHS, fighting for basic care, disability benefits, chasing professionals, it’s pretty disgraceful, we as a family have been put through hell, called liars told we are fabricating our daughter’s condition, which is absolutely ridiculous, the ignorance and lack of education surrounding this catastrophic, debilitating rare disease is as bad as the disease itself, knowing this man made condition could have been stopped is heart breaking’.*

In determining this Review, Baroness Cumberlege now has a unique opportunity to give those affected by FVS, including those represented by OACs and FACSaware, a proper hearing of their concerns. Those concerns relate both specifically to Sodium Valproate and the regulatory and legal failings exposed by the history of FVS.

### *Is a Public Inquiry Justified?*

It has been readily acknowledged by the Public Inquiries Select Committee<sup>94</sup> that, *‘the question of whether and when to hold an inquiry is always problematic’* [45].

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<sup>93</sup> As per victims’ statement set out in **Appendix A** of this submission.

<sup>94</sup> <https://publications.parliament.uk/pa/ld201314/ldselect/ldinquiries/143/14306.htm>

In seeking to throw light on this problem, an Advice Note produced by the Cabinet Secretary in 2010<sup>95</sup> identified certain common characteristics that were common to previous inquiries, including:

- Large scale loss of life (albeit the Cabinet Secretary recognised that Inquiries had looked at single deaths, e.g. Victoria Climbié, as well as large scale loss of life cases, e.g. the Shipman Inquiry)
- Serious health and safety issues
- Failure in regulation
- Other events of serious concern

It is submitted that, all of these characteristics are met in the context of regulatory failures concerning Sodium Valproate provision in the UK. In our submission, the experience of FVS in the UK constitutes a significant widespread harm that could have been avoided but for the inadequate and delayed regulatory response of the UK Government and the responsible manufacturer.

We suggest that an Inquiry into the long term regulatory and legal systemic failures to investigate the causation of FVS by Sodium Valproate, offers an opportunity of a reformed approach to the way in which pharmaceuticals and medical products are regulated; this may be a significant opportunity as we exit the EU and its wider regulatory context.

It may also be opportune to examine the structure of our licensing of pharmaceuticals and medical products in order to determine why it is that funding the 'externalised' cost of adverse consequences to users of these products falls always upon national and local Government, rather than upon the profit generating manufacturer. The obligations we have in mind are the costs of:

- supporting injured children through NHS and Local Authority social care
- supporting injured children through payments of benefits

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[https://www.gov.uk/Government/uploads/system/uploads/attachment\\_data/file/60808/cabinet-secretary-advice-judicial.pdf](https://www.gov.uk/Government/uploads/system/uploads/attachment_data/file/60808/cabinet-secretary-advice-judicial.pdf)

- support of injured children with intellectual as well as physical impairments through the provision of Special Education
- support for those who when they achieve majority, lack capacity and need lifetime care support as adults from Local Authority Social Care and the NHS
- support for the parents of children who are compelled to be their child's carer and who are unable to return to paid work
- litigation pursued against NHS practitioners in the stead of Manufacturers who for systemic and funding reasons are often too expensive and/or too difficult to sue.

Indeed, in large product liability group actions in future, consideration should be given to whether or not a Government body should be a party to litigation against pharmaceutical or medical products manufacturers specifically to seek recovery of these costs.

Alternatively, whether as a condition precedent of product licencing, manufacturers should provide financial guarantees (or at least suitable commercial indemnity insurance based on numbers of patients prescribed their drug or using their medical product) to cover such contingent costs. For example, in Nordic countries a Manufacturer Levy scheme is used to resource a centralised Medical Devices and Pharmaceutical Injuries Compensation Scheme for the benefit of all those injured by products cleared for sale in Nordic markets, at the expense of all Manufacturers who access these markets<sup>96</sup>. FVS campaigners have suggested a tax placed on profits of products at a rate that relates to the severity and frequency of adverse reactions.

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<sup>96</sup> <https://books.google.co.uk/books?id=v-M4DwAAQBAJ&pg=PA6&lpg=PA6&dq=Nordic+Compensation+Scheme+Manufacturer+Levy+product&source=bl&ots=2fj7KuXWCs&sig=iKqIqCSrLo2SvshQLbAAyEqV7Ug&hl=en&sa=X&ved=0ahUKEwik2p3X8IDaAhUEIsAKHSPvDIYQ6AEIKTAA#v=onepage&q=Nordic%20Compensation%20Scheme%20Manufacturer%20Levy%20product&f=false>

### *The suggested remit of an Inquiry*

In terms of the remit of an Inquiry relating to Sodium Valproate, according to the Institute for Government<sup>97</sup> there is an expectation that inquiries will seek to answer at least 3 questions:

- 1) What happened?
- 2) Who is responsible?
- 3) What can we learn from this?

As set out in this submission, all 3 questions remain unanswered in the context of the regulation and marketing of Sodium Valproate in the UK. In summary:

- **What happened?** Charities and campaigners are still seeking a full account of exactly what was known by the Government and Sanofi, prior to its introduction to the UK market in the 1970s. Documents published in print media suggest that decisions were made to not publish full information about the teratogenic capacity of Sodium Valproate, but those affected by this drug have had no opportunity to review or interrogate those documents: the focus of stakeholder involvement initiatives, as described in Section 15 below have been forward looking, concentrating on what can be done in the future, not seeking to analyse what has happened in the past. It is vital that campaigners achieve access to medicine regulation files held in the National Archives, access to evidence cited in successful and unsuccessful legal actions and access to internal documents and information held by manufacturing pharmaceutical companies; and that all such material will be made public. The best framework to facilitate this comprehensive interrogation of all relevant information is through a properly mandated Public Inquiry
- **Who is responsible?** The fact that no litigation has been progressed in relation to Sodium Valproate because of the Legal Service Commission's 2010 decision to withdraw legal funding from claimants has frustrated campaigners' efforts to establish responsibility and to get their voices heard through the mechanism – the EU Product

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<https://www.instituteforGovernment.org.uk/sites/default/files/publications/Public%20Inquiries%20%28final%29.pdf>

Liability Directive - specifically designed to enable them to do so. For more than 25 years campaigners have sought answers and accountability from the Regulator and the Manufacturer, but none have been forthcoming; and,

- **What can we learn from this?** The Sodium Valproate story is a particularly telling example of an unsafe product that has been licensed and relicensed onto the UK market without adequate warnings as to the safety of the product. During its long 'life' so licensed, there have been significant periods of time – most obviously 1982- 2004 – when there has been a significant time lag between the identification of a risk and the sharing of accurate information about that risk both with those taking the drug and those charged with prescribing it.
- The persistent failure of the MHRA and its predecessors to properly protect UK consumers has, from time to time, been exposed in historic cases such as, Thalidomide, iatrogenic CJD, and infected Blood products. These failures were not anticipated or prevented by Regulators but had to be exposed by lawyers .
- This continuing failure to anticipate remains a fundamental issue within the current regulatory regime - typified by more recent disasters like PIP Breast Implants, Vaginal Mesh and Metal-on-Metal hips. *Data regarding HPV vaccine is accumulating and campaigners are concerned that the early warning signs are again being ignored. Complaints have been made due to unfavourable research studies being excluded from EMA PRAC reviews into Gardasil and Cervarix.*  
<http://nordic.cochrane.org/news/complaint-filed-european-medicines-agency-over-maladministration-related-safety-hpv-vaccines>
- The UK Government's repeated failure to learn from these tragedies, and the continued exposure of UK consumers to unnecessary harms arising from poorly regulated pharmaceutical and medical products, suggests that a more fundamental inquiry must now be undertaken into how the current regulatory regime can be rendered fit for purpose, that is - capable of protecting UK consumers and restoring public confidence in the UK regulatory system.

## *The Time for a Public Inquiry is now*

In announcing the Government's decision to order the current review, Mr Hunt asked; '*how [do] we regain the trust of families deeply scarred by these issues.* He went on to say that: '*We can do it in two ways: first, by being open and transparent in everything we do in this process so that they can see we want to get to the bottom of it as much as they do; and secondly by recognising the fundamental issue that in the past when we have assessed these clinical medical safety issues the voice of patients has not been as strong as it should have been. We have to put that right.*'

In our submission, the best forum to ensure that patient's voices are now heard, and to achieve the transparency and rigour that has been conspicuously lacking within the UK regulatory system, is through a Public Inquiry. In the wake of the metal-on-metal hips scandal, the PIP breast implant scandal, and the ongoing campaigns of patients affected by Primodos, Sodium Valproate, Vaginal Mesh and HPV vaccine, public confidence in the UK regulatory system is at an all-time low. The only way to put that right is through a properly constituted Public Inquiry with sufficient powers.

## **Section 10: Crucial Features of a FVS Public Inquiry**

In our submission, the following are crucial features of any Public Inquiry that might be ordered in relation to FVS:

- Judicial Leadership
- Independent clinical and technical advice informing that Judicial lead
- Suitable powers of disclosure from both public and private sector sources
- Suitable powers to require witnesses to attend and give evidence under oath
- Simultaneous transcription of evidence which is published daily on a fully public accessible website
- Representation of all interested parties on an equal footing
- An initial round of fact finding and live witness evidence

- The making of interim factual findings and the notification of any criticisms in **Salmon** letters
- Submissions from all interested parties on the interim findings of fact
- A second round of evidence based on the interim findings, responses to the **Salmon** letters and first round submissions
- Final submissions
- Full report

To achieve this in a reasonable timescale, the Inquiry will need a properly resourced secretariat.

## Chapter 3:

### The Urgent Moral Case for Compensation

This chapter focusses upon meeting the specific clinical and psychological needs of those affected by FVS; outlines the moral case for the creation of a Compensation Scheme for those affected by FVS; looks at comparable Compensation Schemes within the UK; and looks at the possible form and shape of a suitable Compensation Scheme.

The urgent need for meaningful compensation is expressed through the compelling parents' statements at **Appendix A** which we would urge Baroness Cumberlege to read in full. We note in particular the financial burden already shouldered by those families affected by FVS and their concerns for the future:

*'I worry about the future, I worry about what will happen to my gorgeous little girl, when I'm gone, we feel hopeless'.*

*'I have lost our house due to the cost of caring for a child with FACS, we had a mortgage before all of this started but increasing medical expenses, there was no way out'.<sup>98</sup>*

### Section 11: The Specific Clinical and Psychological Needs of those affected by FVS

As a consequence of FVS victims and their families are left with complex emotional, clinical, social, and welfare needs that they must currently navigate alone without access to injury specific funding or assistance from the UK Government or manufacturer.

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<sup>98</sup> Please see victims' statements at **Appendix A**.

The aim of this section of our submission is to:

- Outline the difficulties that those with FVS currently face on a daily basis, looking in particular at the physical, emotional and social impact of FVS for those directly affected, their families and their carers.
- Provide some 'real-life' context for the Review by sharing the experiences of FVS sufferers whom OACs and FACSaware represent; and
- Provide a very loose indication of the financial burden imposed on the individual and the state as a result of FVS.

FVS manifests itself in a number of ways. It may be that an individual with FVS presents with just one symptom such as spina bifida or, as is more often the case, with a constellation of symptoms and conditions. Consequently, the aids, adaptations and support that a person with FVS may need will vary significantly. The aim of this section is to depict the difficulties that those with FVS relentlessly face on a daily basis but it is important to note that this is not a situation where one size fits all. As such this section does not purport to be a comprehensive account or checklist of the needs of an individual diagnosed with FVS. Such an assessment is only possible through one to one dialogue with all of the individuals affected and upon the instruction of relevant experts such as speech and language therapists, occupational health therapist, social workers and other medical professionals but it highlights areas of most significant need.

Some of the individuals affected by FVS and represented by OACs and FACSaware have provided their written experiences for the Review to consider. These are collated at **Appendix A**.

The complexity and importance of an FVS diagnosis is expressed by one mother who recalls:

*“The school wouldn't believe the diagnosis of Fetal Valproate Syndrome so neither did social services. They decided we must have Munchausen's by Proxy and our children were put on the 'at risk' register. It was a terrifying and humiliating two years. If we went to any appointments that were medical or educational then it came up on the*

*screen.....we were marked. It didn't matter that our boys had a diagnosis from a top geneticist who was a specialist in the field of Fetal AntiConvulsant Syndrome.”*

The information provided within this section of our submission is intended to provide the Review with a better understanding of the range of complex challenges and needs that, as it stands in the UK, those directly affected and their carers currently face without access to funding or support from central Government.

### *The physical impact of FVS*

#### ***i. Spina bifida and other mobility impairments***

It is well known that spina bifida<sup>99</sup> may cause paralysis of the legs or other nerve damage affecting muscle control, resulting in significant mobility problems. Depending upon the degree of the paralysis or muscle weakness an individual who has spina bifida may need to use orthotics, ankle supports and or crutches to assist them in their mobility. It is also not uncommon in more severe presentations for an individual to require a power wheelchair for getting around.

Other necessary aids will include standing devices, splints, pressure-redistributing seats, adapted vehicles and Lycra orthoses to support and improve function and stability for the individual. Obtaining the correct aids and equipment can be an ordeal in itself for individuals with impairments. Barriers include funding and the requirement to physically attend numerous appointments.

Patients with spina bifida often have a number of other health problems that further complicate the condition. For example, their bones may not develop as they should and result in fractures and bone malformation which may lead to scoliosis. An individual may also develop bladder and or bowel problems. These present a completely different set of challenges that are complicated further by muscle weakness and or paralysis. Not detracting from the particular

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<sup>99</sup> Similar problems and need may also arise in other impairments such as cases of limb malformation. We have taken Spina bifida as an example because of its prevalence resulting from FACS.

needs and stresses in managing incontinence, personal hygiene, and all day to day activities, which are much easier to maintain where there is no physical impairment. Particular consideration needs to be given to the extent to which an individual is able to weight bear. The physical difficulties may require the need for a single personal assistant to provide support throughout the day. In alternative circumstances it may be that an individual requires the support of two personal assistants and access to a hoist. Funding for a personal assistant is usually dictated by the local authority and, in an era of cuts, tends to fall short of the amount required to pay an assistant for the hours needed. On one occasion an adult individual spoke of being advised to wear nappies on an evening instead of being offered night time support to assist with going to the bathroom.

In addition many individuals with spina bifida also present with hydrocephalus<sup>100</sup>. The excess fluid on the brain caused by Hydrocephalous may result in cognitive impairments and neuro-disabilities.

## ***ii. Autism, Asperger's syndrome and Neuro Developmental Delay***

Cognitive impairments and learning difficulties as listed above not only manifest through Hydrocephalous but are significant frequently occurring symptoms of FVS. The impacts of these conditions and syndromes also have an adverse effect on an individual's physical abilities, some of which are similar to the barriers a visible physical disability imposes. These may include difficulty feeding, reading, hearing and speaking. Invisible impairments can have an equally adverse, if not at times more adverse, effect on an individual's life and often require the support of a personal assistant to support them with their daily hygiene, basic routine, educational achievements and social engagements.

Accessing appropriate treatment is made still more difficult by the fact that many of the relevant physical therapies required by someone with FVS require a level of comprehension by the patient in order for them to access and benefit from the therapy, examples include eye sight tests, audiology assessments, physiotherapy, speech and language exercises, learning to use adapted equipment and behavioural management strategies.

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<sup>100</sup> <https://www.nhs.uk/conditions/hydrocephalus/symptoms/>

The complexity of those impairments and the current lack of provision to assist with them is very well expressed through a letter included in **Appendix A**, which has been drafted for inclusion in this submission by a young FVS sufferer, who concludes:

*“I wish there were people to talk to me – to help me learn how to work around my problems, to accept who I am, to learn how to work, how to play, how to live. I’ve found a majority of the decisions in my life have occurred at the behest of someone who had only ever known me as a name and a number on a piece of paper.”*

### *The Social Impact of FVS*

What those without impairments often fail to see is the wider social impact that even a minor physical, cognitive and or mental health impairment may have on the individual and those around them. A report published by Scope in April 2014 refers to this as ‘*the financial penalty on life*<sup>101</sup>, as it is often the case that assistive technology and equipment that enables an individual to lead a full and active life is prohibitively expensive. Many parents are currently experiencing services being withdrawn due to being reassessed for Personal Independence Payment (**PIP**). Mobility vehicles, respite and personal care budgets have been removed. Families are left isolated, unable to access society and at risk of developing poor mental health.

Beyond the physical boundaries there are the social interaction difficulties that so many people with FVS experience. These misunderstandings make it very difficult for individuals to form long term friendships, sexual relationships<sup>102</sup> and maintain gainful employment.

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<sup>101</sup> <https://www.scope.org.uk/Scope/media/Documents/Publication%20Directory/Extra-Costs-Report.pdf?ext=.pdf>

<sup>102</sup> For individuals with physical dysmorphic conditions and or incontinence problems there will be the added concerns and anxiety that they have surrounding these issues alongside their inability to read social situations. Further, this does not address the barriers to having one’s own family.

### *The emotional impact of FVS*

Inevitably, there are significant emotional consequences of the physical and social difficulties experienced by an individual with FVS.

It is a well-known fact that those who suffer with visible physical impairments are conscious of their impairments which adversely affects their confidence, this can be worse for individuals with facial deformities. The same is true for individuals with cognitive impairments and neuro-disabilities. An individual may be equally worried by their intellectual performance as they are about their appearance.

There will be significant stresses placed on the family units as a whole. The obvious stresses are those caused by the increased financial burden and we are aware of a number of cases where the loss of income arising from a diagnosis of FVS has resulted in the loss of the family home. A family however will also have less time, if any, for enjoyment of the things that one would usually enjoy such as holidays<sup>103</sup>.

The continual social and physical daily battles can grind an individual, and their family, down. For every piece of equipment, for every hour of support that a person with FVS has to support their daily needs there are usually policies and protocols that have to be understood and followed before they are given access to what they need. A common example is the need of those with FVS to have an Education, Health and Care Plan, this is often not granted or is inadequate and the family have to appeal to the Education Tribunal for the appropriate assessment to be made of an individual's need and the one to one support that they require in school<sup>104</sup>. This process is not merely the completion of a form but it involves a multi-disciplinary approach to understanding a child's needs, it often requires legal representatives to help navigate the law and it can take months and years of work by dedicated parents.

Parents may have to give up work to be able to offer the support that a child with FVS needs. It is often the parents who have to take time off work to attend medical and other

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<sup>103</sup> Any trips away usually come with additional costs including; travel insurance, accessible vehicles, adapted accommodation and often paying for an assistant to come too.

<sup>104</sup> The reliability of, and availability of funding for, personal assistants present other daily stresses as does the fight for the other aids referred to above.

appointments. It is a parent who lives with the constant fear that their child may hurt themselves or others. This may lead to financial and matrimonial stresses.

### *The particular needs of mothers caring for children with FVS*

With all of the above in mind it must be remembered that the mother of a child with FVS is managing her own epilepsy or *Bipolar disorder* at the same time<sup>105</sup>. We have been told of one family where the child with FVS is also the carer for their mother who has epilepsy<sup>106</sup>. This situation is one of the distinctive features of FVS and exposes the very significant financial and emotional costs of FVS in the UK where those affected do not have recourse to a central compensation fund.

Some of the symptoms of epilepsy include seizures, loss of consciousness and anxiety<sup>107</sup>. Any one of these symptoms can put a young child with FVS, in the care of an epileptic parent, in danger. The complex needs that individuals with FVS have, the hard work required getting the correct diagnosis and the support that they need is so much more difficult when you have similar problems of your own. A mother who has epilepsy and a child diagnosed with FVS has to balance not only their medical and social appointments but also those for their child. This is further complicated by the fact that many individuals with epilepsy cannot drive and the problems that their children have means that they cannot take public transport. *Removal of the mobility component of Disability living allowance or Personal independence payment does not improve their situation.*

It should be noted that feeling tired can trigger a seizure<sup>108</sup>. Any mother will report the effects of sleep deprivation whilst their child is teething but mothers of children with FVS report that their children did not sleep as a baby as a result of their impairments. In addition to their children not sleeping, the constant worry and anxiety of the repeated daily challenges lead to sleep deprivation and tiredness.

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<sup>105</sup> See Chapter 1 above for a list of the impairment s for which Sodium Valproate is prescribed

<sup>106</sup> It must be remembered that many individuals with FVS have anxiety disorders that may be made worse as a result of their concerns for their mothers' wellbeing.

<sup>107</sup> <https://www.nhs.uk/conditions/epilepsy/symptoms/>

<sup>108</sup> Ibid.

One campaigner with epilepsy who is a full time carer for her daughter who suffers FVS points out:

*Epileptic seizures can be triggered by many different things depending of the type. Stress is a common trigger that increases the risk of an epileptic seizure looking after a FACS child is increasingly stressful, for example continuous battles with SEN services and local authorities, continuously explaining sodium valproate syndrome to professionals and teachers, other parents staring at your child because of constant tantrums in public places. The frustration of nobody listening to your opinion at school because they are the professionals you're just the mother<sup>109</sup>*

Further, there are women who blame themselves and their impairment(s) for their child's impairments and the neo-natal deaths and still births that they have suffered. Many women report finding it extremely difficult to become pregnant and have suffered a number of miscarriages most probably related to their medication. The consequent severe levels of stress, constant worry and isolation may also result in a diagnosis of depression on top of their other difficulties.

The accounts in **Appendix A** attest to the frequency of miscarriage, depression and isolation suffered by the mothers with epilepsy represented by this submission who also care for their children with FVS.

One mother reports feeling particularly anxious that she would have a seizure whilst holding her baby in the early days after birth. In light of this she relied more than she ordinarily would have on her own mother for support. This anxiety caused, by the fear that a mother with epilepsy may harm her own children through seizure, was a factor mentioned by 9 out of 10 respondents to a survey conducted by OACS. A number of the respondents report that they were not allowed to bathe or feed their children because of the dangers associated with having a seizure. Health Visitors have been essential to many families in the first year of the child being born. The challenge faced now is getting access to a Health Visitor as many posts have been cut right across the UK.

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<sup>109</sup> A full account of this experience is included in **Appendix A**.

## Section 12: An appropriate scheme of assessment of needs

This submission is drafted on the basis that a Public Inquiry is needed and that when it reports it is likely to provide:

- (a) A full explanation of the history of Sodium Valproate: The risks associated with it before it was marketed, those risks which have emerged in the years during which it has been licensed and the impact upon the lives of the children of unwitting women with epilepsy who were prescribed the drug without knowledge of those risks of the drug.
- (b) Momentum for the creation of an authoritative Diagnostic Pathway to identify individuals affected by FVS, through engagement between patient groups, relevant experts and NICE. This recommendation is given further consideration in Section 15 below.
- (c) A new model for precautionary regulation: Brexit offers an opportunity for a new model which can operate over the next 20 years, predicated on the precautionary principle and mandating candour in risk-warning by manufacturers and regulators towards patients and their treating clinicians.
- (d) A change in attitude towards the pharmaceutical and medical products industry: Acceptance for the first time that the pharmaceutical and medical products sector whilst manufacturing healthcare products, is not an inherently altruistic environment but a commercial profit-seeking industry which needs to be robustly regulated.

On the assumption that this Public Inquiry reaches not dissimilar conclusions, we think it may be helpful to identify a mechanism which could be used to meet the needs of those affected by Sodium Valproate.

### *The Impact of FVS on the UK Economy*

Within the limited time available to prepare this submission, we have not been able to fully analyse the generic cost burden for the state that has been imposed by the legacy of FVS in the UK. It is nevertheless submitted that with reference to the complex clinical, social, educational and welfare issues outlined within this section, if fully calculated, this cost would be very significant.

That cost burden is currently carried by the individuals affected by FVS, their families and through the provision of state funded welfare. To date, in the UK, the manufacturer of Sodium Valproate, Sanofi, has not provided any financial support for the families affected by FVS nor the UK Government. A consideration of the desirability and mechanism for seeking such a contribution from manufacturers can, at this stage, only be made out in principle: nevertheless we set out below a brief analysis of the potential costs associated from just two aspects of FVS, in order to draw attention to the very real need to secure additional financial provision for those affected by FVS in the UK.

Isolating just two aspects of FVS:

- Re Autism; a study published by LSE in 2014<sup>110</sup> (“the 2014 study”) indicated that the care and support of individuals with autism is costing the UK at least £32 billion a year, more than heart disease, cancer and stroke combined.<sup>111</sup>
- Re ASD and intellectual disability (ID); during his or her lifespan was estimated to be £1.5million. The cost of supporting an individual with an ASD without ID was £920,000.

#### *The continued profitability of Epilim for the Manufacturer*

As of 2018, the manufacturer of Epilim in the UK, Sanofi, has provided no financial support to those affected by FVS or, as far as those responsible for this submission are aware, provided any reimbursement of the cost of FVS to the UK Government. This fact sits at odds with the following facts:

- Sanofi is the fifth largest pharmaceutical company in the world, with 81 manufacturing sites in 36 countries.<sup>112</sup>

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<sup>110</sup> The London School of Economics and Political Science

<sup>111</sup> Buescher, A., Cidav, Z., Knapp, M. and Mandell D (2014): Costs of autism spectrum disorders in the United Kingdom and United States of America. JAMA Pediatrics, 168, 721-728

<sup>112</sup> Sanofi’s 2017 Annual Report is available at <https://www.sanofi.com/en/>

- Sanofi's net sales for 2017 were €35 billion and the company has had revenue of €403 billion from 2005 to 2017.<sup>113</sup>
- Sodium Valproate is marketed in over 100 countries and is one of Sanofi's best-selling pharmaceutical products. As such, Sanofi's net sales for Sodium Valproate in 2017 were €443 million.
- From 2005 to 2017, the company has had revenue of €4.837 billion from the sale of Sodium Valproate.<sup>114</sup>
- Sanofi has enjoyed tax incentives from the UK Government for its Research & Development programmes through much of the period during which this drug has been licensed.

In our submission, it is time to investigate the responsibility of Sanofi and the Regulator in the creation and continuation of FVS as a diagnosis in the UK. The objective of that investigation must be to hold those responsible accountable, morally, if not legally, and certainly financially. It must be noted that FVS sufferers and their families in the UK have had to shoulder the clinical, emotional and financial impact of FVS alone, without centralised support.

The cost burden upon local and national Government in the UK and those of its citizens affected by FVS, should, at least in part, be met by its manufacturer, Sanofi.

## **Section 13: The Moral Case for a Compensation Scheme for those affected by FVS**

### *The Moral Case*

As set out in Chapter 2 of this submission, those responsible for this submission maintain:

- The fact of FVS in the UK is the result of a persistent failure on the part of the regulator and manufacturer to ensure that appropriate information was communicated directly to

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<sup>113</sup> This financial information has been obtained from Sanofi's Financial Annual Reports from 2007 to 2017 available at <https://www.sanofi.com/en/>

<sup>114</sup> Ibid.

the patient and to the clinician concerning the teratogenic potential of Sodium Valproate.

- In contrast with other jurisdictions, potential FVS litigants have historically been denied access to justice by the Legal Service Commission's decision in 2010 to withdraw funding for a legal action 3 weeks prior to the beginning of trial.
- Newly available epidemiological evidence, and a favourable decision in the case of *NW v Sanofi C-621/15*, mean that European litigants generally have better prospects of successfully litigating against Sanofi and the incumbent regulators within their jurisdiction: However, for those affected in the UK the prospects of renewed litigation remain relatively poor.

It is now clearer than ever that:

- FVS sufferers and their families have complex needs and are in the unusual position of having to cope with children with often profound disabilities whilst dealing with the fact of their own epileptic condition.
- The NHS, working alongside the families of those affected by FVS, is shouldering a significant cost burden as a result of FVS.
- To date Sanofi, the manufacturer responsible for Sodium Valproate have made very significant profits as a result of their marketing of Sodium Valproate in the UK but have not shouldered any of the costs of FVS.

In our submission it is upon these arguments that the moral case for compensation is based.

#### *The Compensation Fund now available for FVS victims in France*

The French Government has already responded to the moral case for compensation for those affected by FVS, as set out in detail at **Section 13**.

It is understood this is a state funded scheme that recognizes failures on the part of the French Government in the way that Sodium Valproate was regulated and permitted to be

marketed in France. The French Government has reportedly set aside an initial 10.7million EUROS<sup>115</sup> for this fund.

In comparing the actions of the French Government and courts it is important to remember that these authorities have had to deal with the same drug (albeit under a different brand name), the same cluster of injuries ( FVS), the same Defendant, within the same legislative framework by virtue of the European wide Product Liability Directive; and yet, to date, French victims have benefitted from a compensation scheme which assists in meeting the additional financial costs associated with caring for children with special physical, emotional and developmental needs [and provides a fund for potential litigation].

In the UK, as it stands, no such support exists.

## Section 14: ‘No Fault’ Compensation Schemes in the UK

In considering the creation of a Compensation Scheme for FVS sufferers and their families in the UK, we highlight two existing schemes which provide for those injured by Thalidomide and those affected by vCJD: These schemes, described below, are funded both by contributions from the manufacturers responsible for producing the product at issue; and/or the Governmental body that permitted the product at issue entry onto the UK market.

The Thalidomide and vCJD Trust schemes are **not** held out as perfect examples of how a compensation scheme might be structured for FVS victims in the UK. However, details are provided here in order to assist the Review in thinking through how a Compensation Fund might be structured in the UK using these examples of the creative thinking of their time to solve a particular problem.

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<sup>115</sup> <https://www.reuters.com/article/us-sanofi-france-compensation/france-sets-up-fund-for-sanofi-epilepsy-drug-victims-idUSKBN13B1FN>

### *Specific Issue Compensation Schemes*

The 'no-fault' based redress schemes currently and/or historically available in the UK bear testimony to a series of medical/regulatory disasters involving unsafe medicines and other products.

The objective of these schemes is to provide principally financial support to persons injured by exposure to defective drugs/products.

In all instances the question of legal liability has been set-aside or deferred as a result of the institution of the Compensation Scheme: This has, in most instances, saved potential Claimants and manufacturers from the very significant costs of adversarial product liability litigation in the UK. However, the fact of a specific issue Compensation Scheme recognizes the social responsibility of the manufacturer and/or Government to provide extra resources and support to all those who have been injured consequent upon their exposure to the product at issue<sup>116</sup>.

An overview of the history behind each scheme is provided below.

#### *The Thalidomide Trust*

Sodium Valproate has been identified in some media output as the 'new Thalidomide'<sup>117</sup>: That comparison is accurate not only with reference to the teratogenic capacity of Thalidomide and Sodium Valproate, but also with reference to the regulatory failures alleged against the incumbent authority; the heavily discounted settlement of the legal action bought in the UK

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<sup>116</sup> In the interests of space and time this section does not look at other 'no-fault' redress schemes within the UK relating to industrial injuries disablement e.g. mesothelioma schemes, Coal Workers' Pneumoconiosis/COPD and Vibration White Finger: Whilst such schemes are outside of the remit of this submission they are perhaps still instructive reference points for those engaged with this Review.

<sup>117</sup> [http://www.dailymail.co.uk/health/article-3997260/Warning-epilepsy-drug-dubbed-new-thalidomide- Thousands-British-mothers-taking-medication.html](http://www.dailymail.co.uk/health/article-3997260/Warning-epilepsy-drug-dubbed-new-thalidomide-Thousands-British-mothers-taking-medication.html)

against the UK distributor of Thalidomide, Distillers Ltd; and the role of victims' families and campaigners in pushing for proper compensation for all those injured<sup>118</sup>.

### *Route to Compensation: Thalidomide*

The litigation history of Thalidomide is complex, but can be summarized as follows:

- **1962 Request for a Public Inquiry:** In July 1962 28 MPs sought a Public Inquiry concerning Thalidomide. This request was refused. Litigation followed.
- **1968 Settlement:** The parents of 65 children injured in utero by Thalidomide exposure originally brought a legal action against the manufacturer of Thalidomide Distillers UK Ltd. In 1968 Distillers offered to settle those 65 cases prior to trial for a litigation discount of 60%. Beneficiaries were awarded £5-45,000.00 depending on the severity of their injuries. This settlement only included the 65 issued cases.
- **1973 Settlement:** A campaign led by the Sunday Times resulted in the extension of the 1968 settlement to include all children who met the criteria for acceptance.
- **Thalidomide Trust:** Subsequently the Trust was set up to provide additional monies to children affected on an annual and exceptional basis. This Trust was funded by additional payments from Distillers UK Ltd and later Diageo plc who bought Distillers. Significant additional funds were provided in 2005 as a result of persistent campaigns by 'Thalidomiders'. Diageo undertakes with the trust a triennial review of Thalidomiders' needs.
- **2010 Government Health Grant:** The Government Health Grant was set up to provide additional funds for Thalidomide victims in recognition of '*the increasing health needs of Thalidomide survivors as they approach older age and that more investment is needed to help meet the complex health needs that can arise*'. The total value of the scheme is £80million to be administered by the Thalidomide Trust. It is understood that this Health Grant will be continued until at least 2022 and is intended to be an expression of the Government's 'deep sympathy for the injury and suffering endured by all those affected by the drug Thalidomide. "*This deal represents our clear acknowledgment that thalidomiders should be supported and helped to live as*

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<sup>118</sup> <https://www.thalidomidetrust.org/about-us/history-of-thalidomide/>

*independent lives as possible, and we hope that this funding will aid that cause and provide an element of long term financial security.”<sup>119</sup>*

*Compensation Scheme Details:*

<p>Source of Funding:</p>	<p>Thalidomide Trust: Manufacturer (Diageo plc)</p> <p>Original settlement and regular needs review.</p> <p>Government Health Grant: Government (until 2022 at least).</p>
<p>Eligibility:</p>	<p>In order to become a beneficiary of the Thalidomide Trust and the Government Health Grant Scheme (for which it is first necessary to be a Thalidomide Trust Beneficiary) applicants have to show that they meet the following criteria as set out in the 1973 Thalidomide Trust Deed: (1) Born in UK; or (2) Mother resident in UK at date of ingestion of Thalidomide; (3) Residence in UK before 22.2.1973 or in other stated territories. (4)Mother ingested Thalidomide; (5) Injuries have been caused by Thalidomide.</p>

<sup>119</sup> <https://www.gov.uk/Government/news/health-grant-awarded-to-victims-of-thalidomide>  
 Published 20 December 2012

<p>Number of beneficiaries:</p>	<p>As at 2018, 468.</p>
<p>Structure:</p>	<p>The Thalidomide Trust is run as an independent charity, with a CEO and a group of paid staff. The staff are supported by a Board of Trustees, who collectively have the discretion to: (1) decide whether an individual can become a beneficiary of the Trust: and (2) decide the value of the annual stipend awarded to a beneficiary.</p> <p>There are appeal processes available within the Thalidomide Trust structure but ultimately decisions rest with the Trustees, who are advised by experts instructed and funded by the Trust.</p> <p>Thalidomiders/Beneficiaries have some voice within the management structure of the Trust through the 'National Advisory Council'.</p>
<p>Value of Fund:</p>	<p>Diageo plc now invests £37.5m in the Thalidomide Trust annually and has agreed to maintain this commitment until 2022.</p>
<p>Individual beneficiary</p>	<p>Allocation of annual funding from the Thalidomide Trust is based upon the severity of Thalidomide related injuries suffered which are scaled from 1-100 in terms of severity. Annual allocation of funds is then made with</p>

allocation:	reference to this score. Each individual's needs are assessed in detail with the benefit of expert reports as necessary. If a beneficiary feels that their needs have changed they can apply to the Trust for reassessment of their allocation. Beneficiaries have access to an Holistic Needs Assessment, managed by the Trust which is intended to monitor all of their health needs, physical, psychological and emotional and to make appropriate provision as these needs change. Annual allocation of funds is then made with reference to this score.
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*Variant-Creuzfeldt Jakob Disease (vCJD) Trust*

vCJD, the human form of BSE, is a fatal neurological disease associated with a build-up of prion proteins in the brain.<sup>120</sup> It was first identified in the late 1980s, and its link to infected cattle was discovered in 1996.<sup>121</sup>

As of 2017, 178 people in the UK had been diagnosed with vCJD,<sup>122</sup> with the number of deaths peaking at 28 in 2000<sup>123</sup>. Because symptoms can take several years to develop, it is estimated that many more people may be carrying the disease. This may be as many as one in every 2,000 people in the UK.<sup>124</sup>

<sup>120</sup> <https://www.theguardian.com/society/2014/jul/24/risk-infecting-surgery-patients-cjd-not-taken-seriously-mps>

<sup>121</sup> <http://www.cjd.ed.ac.uk/>

<sup>122</sup> <https://www.newscientist.com/article/2118418-many-more-people-could-still-die-from-mad-cow-disease-in-the-uk/>

<sup>123</sup>

<https://www.theguardian.com/uk/2008/aug/03/bse.medicalresearch>

<sup>124</sup> [https://www.gov.uk/Government/uploads/system/uploads/attachment\\_data/file/186959/risk\\_assessment\\_Feb\\_2013.pdf](https://www.gov.uk/Government/uploads/system/uploads/attachment_data/file/186959/risk_assessment_Feb_2013.pdf)

### *Route to Compensation Scheme:*

In summary:

- Families of vCJD victims campaigned for a Public Inquiry from 1996 onwards.
- The BSE Inquiry was constituted in 1997.
- Litigation against the Government was initiated in **1997** to preserve the limitation position for the victims families.
- This BSE Inquiry considered the need for a care package for those suffering vCJD and revealed an urgent need for improvement in the consistency of NHS and Local Authority provision of care for vCJD victims
- Following the recommendation of the BSE Inquiry, a Trust fund was set up by the Department of Health to compensate victims of contaminated meat products, the first death from which was reported in May 1996. A national care scheme was also inaugurated, operating from the CJD Surveillance Unit in Edinburgh

### *Compensation Fund Details:*

Source of Funding:	Government/NHS
Eligibility:	Confirmed diagnosis by the CJD Surveillance Unit at the Western General Hospital in Edinburgh who act as Special Advisors to the Trustees.
Number of beneficiaries:	At present 178. Fund is currently structured on the basis of 250 beneficiaries. The terms of the fund will be revised if the number exceeds 250 beneficiaries.
Structure:	Managed through Trustees with a specialist clinical team (the CJD Surveillance Unit) appointed to advise and diagnose potential beneficiaries. Trustees are appointed by the Government.
Fund Value:	The Government set aside £67.5million to compensate those affected. This £67.5m was divided into a Main Fund (£62.5m) and a Discretionary Fund (5m eventually increased to £8m).
Individual Beneficiary	<ul style="list-style-type: none"><li>● Trustees are guided by a Trust Deed which sets out terms of provision</li></ul>

Allocation:	<ul style="list-style-type: none"> <li>● Basic award is: <ul style="list-style-type: none"> <li>○ £120-125,000 for each individual claimant – depending on date of diagnosis</li> <li>○ Access to a state funded care package on application</li> <li>○ Compensation for gratuitous care provided assessed on an individual basis</li> <li>○ Compensation for carer’s loss of earnings package assessed on individual basis</li> <li>○ One off award for ‘Experience of Family’ ranging from £5-£10,000</li> <li>○ Compensation for loss of dependency – assessed on an individual basis</li> <li>○ Funeral expenses covered</li> <li>○ Provision of mortgage protection and life insurance on application</li> <li>○ Access to a Particular Hardship Fund for additional extraordinary expenses e.g. counselling etc, on application</li> <li>○ Loss of Earning claims for individuals – again assessed on case by case basis.</li> </ul> </li> </ul>
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### *Lessons to be Learned?*

There is no simple mechanism available to compensate FVS victims as there would be if they lived in Sweden where a no fault scheme covering all drug injuries operates. The closest comparable scheme we have in the UK is the Vaccine Damage Payment Scheme which has never operated satisfactorily but which could be adapted with sufficient political will.

Assuming however that there might be sufficient political will for a bespoke solution to the problem of compensating FVS victims, then there are lessons to be learned from the two models described above.

Common features of the Thalidomide Trust and the vCJD Trust, that, in our submission, contribute to the success of both compensation models are set out below but a primary concern in the case of FVS is the question of ascertainment of the accurate number of those affected by the condition:

#### ***Effective means of identifying and reaching out to beneficiaries***

- A clear and authoritative **Diagnostic Pathway** that can be used to identify all individuals suffering from FVS and whom, on that basis, may be eligible for compensation.
  - FVS was first identified as a diagnosis in 1978, subsequent research and the development of clinical understanding warrants a review by NICE, involving patient groups and relevant experts, toward the development of a clear diagnostic pathway. This needs to happen now.
  
- A **Retrospective Audit Process** to ensure that all those affected by FVS, but who may not have been diagnosed, to date, have the opportunity to benefit from any compensation package created This audit process might involve:
  - Usage of the historic NHS records to identify women prescribed Sodium Valproate whilst pregnant who may be contacted through their GP.

- Usage of any relevant records held by the UK Pregnancy and Epilepsy Register.

### ***Effective Management of the Scheme***

- Management of the Schemes through an independent Board of Trustees, constituted and acting in accordance with a Deed of Trust that allows exercise of discretion
- Management of the Schemes through a single body that administers funds for all those affected (the four different funds set up for Infected Bloods beneficiaries have led to inconsistency and added substantially to administrative cost).

### ***Beneficiary Enfranchisement***

- In the context of FVS, parents/carers must be involved in planning the constitution and administration of any such fund. The contribution of the Human BSE Foundation in both lobbying for and helping constitute the vCJD Trust is a good example; as is the contribution made by beneficiaries of that Trust, who subsequently served as Trustees of the Trust and who brought experience and insight into that difficult task.
- A review mechanism by which beneficiaries can appeal any decision made by the Trustees without incurring extensive additional costs.

### ***Appropriate Resources***

- The likely numbers to be compensated imply that any bespoke Trust constituted will need a significant secretariat and annual budget to meet the cost of defining and assessing payable compensation; it will also need access to the best clinical advice and research information.

### ***Discrete and Dynamic Funds***

- It will need a discrete fund and – since many of those to be compensated have lifetime needs to meet. The likelihood is that it may need further significant capital payments. In the case of the Thalidomide Trust, the capital payments made to establish the Trust and at various times since, have enabled the Trustees to develop investment policies appropriate to anticipated needs of the overall cohort, to match income to annual expenditure on grant giving to beneficiaries. Further to maintain a careful watch on

annual administrative cost , if the Trust is to be truly independent it should be equipped with a sufficient fund at the outset to enable it to derive income from invested capital and attempt to match compensation payments from that income. A major lesson from the Thalidomide Trust is that the funds with which the Trust is established need to be adequate and predicated on meeting lifetime needs for injured children with conventional (rather than impaired) life expectancies.

- The running costs of the Trust should also include providing funds to ensure that regular updating Holistic Needs Assessments with **each** beneficiary maintain a clear understanding of the health needs of the overall cohort supported.
- Both Schemes are dynamic – i.e. able to access increased funding in line with the changing needs of their beneficiaries as a group and as individuals (especially the Thalidomide Trust); and the number of beneficiaries (i.e. the vCJD Trust).
- Both Schemes allocate funds on the basis of a detailed individual needs assessment undertaken in consultation with appropriate clinical and care need specialists and make payments on an annual basis to support those with long term care needs as well as ‘one off’ payments to meet specific equipment or other short term needs.

#### ***Independence from Central Control by Government or Department of Health***

- Both are run independently of the Government or Department of Health but are independently audited; the likely scale of this proposed Scheme, in our view, requires more than auditing and charitable oversight and should include direct annual reporting to the House of Commons Health Select Committee.
- Both funds have specific delegated legislation which enables grants to be made to beneficiaries without incurring ‘claw back’ of statutory benefits. Any scheme for FVS would have to mirror this approach and should aim to establish a similar approach to the cost of social care.
- Both schemes have experienced clinicians and lawyers as trustees which readily enables the marshalling of external expertise in the conduct of the Trust’s business e.g. establishing eligibility and of maintaining control of funds in the face of lost capacity. It will also be important for parents/carers of FVS sufferers to have maximum involvement in the work of such a scheme. Experience in the vCJD Trust points to the significant advantage to be gained from recruiting Trustees from amongst the parents

of beneficiaries, who will add experience of living with and caring for this condition, to the more general experience of lawyers and doctors. As with the Thalidomide Trust – whose National Advisory Council has proved such a valuable voice on behalf of Thalidomiders – the proposed Trust must also provide a mechanism for those parents and beneficiaries able to do so, to assist the Trustees to direct the resources of the Trust in the best way to improve the lives of FVS sufferers

Any Trust structure must be adapted to empower parents/carers in order to embody the fundamental truth expressed by one mother of an FVS sufferer, who told us:

*‘The one thing I learned is that you are your child’s best advocate and that is a skill that has to be acquired very quickly’.*

These advocacy skills have provided critical insight for the MHRA and EMA in reappraising their approach to warning women with epilepsy of the real risks associated with Sodium Valproate, as set out in **Section 15**. In the same way, there is hugely important insight to be gained, about the day to day impact of FVS, from those who live with it and have to deal with it every day of their lives.

### *Interim Provision*

Finally, in considering the mechanism for compensation, it must be recognised that some of those affected by FVS have been seeking compensation for more than 40 years. As such, recognising the urgent necessity, but also the complexity of setting up a formal compensation scheme, this submission urges consideration of the following interim ‘catch up’ measures, pending the institution of a comprehensive compensation scheme:

- The ring-fencing, so far as is practicable, of local authority budgets to ensure continued adequate provision of health, education, community services and wider welfare needs for those already diagnosed with FVS;

- Funding and access to private health care schemes for all families affected by FVS; and/or
- Prioritisation of appointments for FVS sufferers *and their parent family carers* with specialist services within existing NHS structures.

### *The Scale of a FVS Compensation Fund?*

The scale of the task of quantifying the compensation required for FVS sufferers and their families is currently hard to estimate because there are no accurate figures to establish the number of FVS patients,<sup>125</sup> but given Sodium Valproate has been licensed since the 1970s and has had accurate risk warnings from (perhaps) 2005, it can be assumed that there will be

<sup>125</sup> Norman Lamb MP asked the following Parliamentary Questions in March 2018 (echoing questions posed in 2009 by Ben Wallace MP in 2009): Question:

To ask the Secretary of State for Work and Pensions, what estimate he has made of the amount paid out by his Department in benefits to people with fetal anti-convulsant syndrome as a result of the mother being prescribed sodium valproate during pregnancy. (131833) Answer:

Sarah Newton: The information requested is not readily available and could only be provided at disproportionate cost. The answer was submitted on 14 Mar 2018 at 17:20. **Question:**

To ask the Secretary of State for Health and Social Care what information his Department holds on the number of (a) adults and (b) children diagnosed with fetal anti-convulsant syndrome in the UK as a result of mothers being prescribed with sodium valproate during pregnancy. (131830)

**This question was grouped with the following question(s) for answer:**

1. To ask the Secretary of State for Health and Social Care, what estimate he has made of the cost of providing (a) special educational needs and (b) disability support for children diagnosed with fetal anti-convulsant syndrome as a result of mothers being prescribed sodium valproate during pregnancy. (131831)  
Tabled on: 09 March 2018
2. To ask the Secretary of State for Health and Social Care, what estimate he has made of the cost of providing social care for children diagnosed with fetal anti-convulsant syndrome as a result of the mother being prescribed with sodium valproate during pregnancy. (131832)  
Tabled on: 09 March 2018

**Answer:**

**Jackie Doyle-Price:** Information on the number of adults and children diagnosed with fetal anti-convulsant syndrome in the United Kingdom due to pre-natal sodium valproate exposure is not collected centrally. Fetal anti-convulsant syndrome is a non-drug specific condition that relates to abnormalities in children exposed to any anticonvulsant, not just sodium valproate, during pregnancy.

The Department does not collect data about local authorities' expenditure specifically on social care provision for children diagnosed with foetal anti-convulsant syndrome, or on the provision of special education needs or disability support for such children, and no estimate has been made by the Department of these costs.

all age groups between children and middle-aged people in the FVS cohort demonstrating a wide range of existing needs.

At present and until more accurate information about the incidence and nature of Sodium Valproate effect is available, it is probably impossible to do more than suggest the appropriate mechanism of compensation, (as we have done in **Section 14** of this submission), than to attempt to identify the scale of the compensation fund that will be needed.

## Section 15: Better Together

In the final section of this submission we focus upon two of the specific questions raised by the Secretary of State in announcing the remit of this Review:

- *‘whether the regulators and NHS bodies did enough to engage with those affected to ensure their concerns were escalated and acted upon; and*
- *‘whether there has been sufficient co-ordination between relevant bodies and the groups raising concerns’;*

The simple answer to these questions, as evidenced throughout this submission, is *‘no, there hasn’t been’*.

In describing why this Review was necessary, Mr Hunt’s own pre-sentiments echoed this summary assessment: He recognised the extent of disenfranchisement suffered by those affected by medical device failures in the face of Governmental inaction and manufacturer indifference, explaining that:

*“...patients and their families have had to spend too much time and energy trying to access, lobby and influence NHS leaders and Ministers to get a hearing for their concerns. The stress and frustration of campaigning, sometimes in the face of closed ranks and a defensive system, has added insult to injury for too many families”.*

In the specific context of FVS, perhaps uniquely when set against the other products within the scope of Baroness Cumberlege's review, the fact of that 'stakeholder' disenfranchisement has not only added insult to injury for the families involved but has also, in a very literal sense, added **injury to injury**:

### *Adding Injury to Injury*

All of the mothers of children diagnosed with FVS, are themselves women with epilepsy or bipolar disorder. These women, many of whom are represented by OACS Charity and FACSaware have been compelled to pursue exhausting and stressful campaigns to protect their children's rights when nobody else would listen. This has exposed these women to:

- **Serious increased health risks**, as convulsions are offered triggered by stress and exhaustion.
  - This stress was exacerbated for many by the failure of legal action.
  - Those playing active roles within the groups represented by this submission are, in many cases, forced to cope with their own disability and those of their children whilst also dealing with the mental and physical strain of managing highly effective action groups.
  - In the words of one mother affected:

*"..The demands of the court case and of the charity meant that Fetal Valproate Syndrome had completely taken over our lives. We were continually filling out paperwork either for the trial or for OACS. We had the strain of our battles with social services and schools alongside this. The more we discovered the angrier I became at how my childrens' lives had been changed so much because it was decided we shouldn't know the risks associated with the medication we were taking"*

- **Public stigma and prejudice** which continues to be attached to disability in 21<sup>st</sup> century Britain.

- By being compelled to head up vocal and high profile action groups these women have had to draw attention to their disabilities and those of their children.
- One campaigner has likened the public exposure of her epileptic disability as the “coming out” process that LGBTQ have to go through: She explains that whilst *‘prevailing attitudes to epilepsy have changed over time it is far from open and inclusive about the issue’*.
- In the words of one young adult, who suffers autism and other clinical problems as the result of FVS:

*“...To get the support any of us need, we need to put our weaknesses on display, and inform those who would judge us that we are weak. We need to not only be able to confront our weakness, but in order to get any help, we have to publicly and shamefully declare our failings in body and mind. It is devastating. It is especially devastating when even after all this, when having bared your chest and your vulnerabilities for all to see, you are still denied help”.*

A mother, full time carer and front-line FVS campaigner has told us:

*“...”FVS behaviours are often disruptive, it is not bad parenting, it is not a naughty child it is a syndrome that cannot be cured. We get stared at, tutted at, excluded from events because our child might not fit in and inclusive provision that we have relied on is now being cut as Local Authorities and NGOs lose their funding. Some of our children have been excluded from school due to them being violent to the teacher or other children. Many of us are no longer welcome at family events as our children ‘play up’ and are ‘destructive”.*

- **Public exposure of misplaced, but understandable, feelings of guilt** for having inadvertently exposed their children to the teratogen Sodium Valproate as a result of the failures of the manufacturer/regulator and clinicians involved to warn.
  - One mother affected describes, the *‘overwhelming feeling of guilt though, the thought that I was the reason my children struggled so much was like a knife*

*going through me, and even though I had followed all the advice given to me it was a feeling that would never fully leave me'.*

- The word 'guilt' is evident throughout the personal accounts in **Appendix A**.

What sets the FVS scandal apart is what we describe as the '**Double Disability**'. Mothers, themselves disabled by epilepsy and dependent upon anti-convulsant drugs to live normal lives, must care for their children who have been disabled by FVS caused by the drugs that make those normal lives possible.

**These disabled women then have not only to manage their own debilitating condition but have also to care for their children, as mother, carer, support worker and advocate. This isn't a case of adding insult to injury but of injury to injury; this is the reality of the Double Disability that the mothers' of FVS children are forced to live every day.**

### *From Injury to Action*

The campaigning women and their families who are represented through this submission had two options when faced with the reality of FVS and the intransigence of MPs, the regulatory bodies and the manufacturer:

- To accept that position and to walk away; or
- To campaign in order to ensure that other women, and their children, were protected from the harms associated with Sodium Valproate, and to campaign for their children's rights.

They chose the latter path: The groups OAC Charity and FACSaware are the embodiment of that refusal to accept inaction. Indeed, in a recent survey carried out for the EMA Public Hearing, most members felt that they had been supported more by these self-help groups than by any other statutory services.

After the failed legal action and years of emailing MPs and meetings in Parliament that led to no real change, campaigners joined together through social media platforms like Facebook

and Twitter: In this way, their outreach was no longer reliant upon engaging politicians and other officials. Campaigners banded together and made direct approaches to the MHRA; firstly by email, then by sending exhaustive packs of information which showed that the warnings and practices associated with Epilim were out of step with the latest scientific knowledge and research; and finally by direct action with campaigners and their families demonstrating outside the offices of the MHRA.

### *Acting Together for the Future*

In 2013 the voices of campaigners finally broke through and the MHRA invited campaigners to sit with the MHRA in order to work together and ensure safer warnings and prescription policies for Sodium Valproate. This resulted in the MHRA creating a Valproate Stakeholders Network, with a brief to discuss prevention of harm, engaging families, charities, clinicians and royal colleges/societies. This network quickly developed into a real forum for change through the careful chairmanship of Dr June Raine, Director of Pharmacovigilance at the MHRA.

The impact of this group is evidenced in the eventual referral of Sodium Valproate to the EMA and the consequent first Public Hearing into a medicine by the EMA. Women with epilepsy, bipolar and migraine across Europe have benefitted from the concerted efforts of the campaigning women represented by this submission, as evidenced in the regulatory developments set out in **Section 3**.

As at the date of this submission the EMA has recommended a raft of counselling, educational and prescription practices that will better ensure that no woman with epilepsy inadvertently exposes their child to the risks of FVS (**Section 3**). This is the direct result of campaigners' action working alongside the MHRA, combining the extensive knowledge and commitment of these campaigning families with expertise of the professionals brought together through the MHRA.

Of course, it goes without saying that these changes could have been effected earlier if the Government of the day and regulators had been willing to listen to campaigners, but the focus

of this final section is, at the express request of OACS Charity and FACSaware about looking to the future.

Constructive 'stakeholder' engagement has become an important part of contemporary political practice for example:

- In education (e.g. OFSTED now seek views of parents and children);
- In health (e.g. CQCs now routinely use patient questionnaires); and
- In issue specific contexts, such as the '*Time to Change – Time to Talk Day*' campaign, championed by the Secretary of State for Health and intended to push for an end to stigma and discrimination of people with mental health illnesses<sup>126</sup>.

The success of the Valproate Stakeholders Network in persuading Regulators to properly describe the risks of Sodium Valproate– and thereby bring about a real change in the prescribing behaviour of neurologists and GP's -provides further evidence that patient consultation is not only important but also has the power to effect real and lasting change.

On this basis **FACSaware** have identified the following key policy goals, which could be effected through the expansion of the MHRA Valproate Network model into other spheres of policy making, including:

- **Education:** Teaching about teratogens needs to be part of the Statutory National Curriculum. Educational materials need to be produced and endorsed by DfE and DoH. This is currently inadequate as its part of KS3 & 4 Science and Non statutory PSHE KS3 & 4 through the Drug Use and Misuse lessons.
- **Research:** Using the 100k Genome project to collect information about teratogens
- **Regulatory:** Continued promotion of the MHRA Yellow Card at community exhibitions and online.
- **Health:** Wellness in pregnancy public health promotion:

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<sup>126</sup> Initiatives were also encouraged at a local level: E.g. Community events include Leicester Time to Change. [www.leicestertimetochange.co.uk](http://www.leicestertimetochange.co.uk)

- Its purpose is to make men and women aware of the importance of making your body as healthy as possible before conception by making lifestyle and dietary changes to improve general wellbeing in preparation for sperm and egg production and providing a safe place for the fetus to grow. This has important synergy with the Outcomes for Better Births report by Baroness Cumberlege.

**OACS Charity** have also identified key measures to prevent another tragedy of this type happening again, as listed below:

- Institute a successful **health care pathway** with a wide range of professionals and groups
- **Securing funds to:**
  - Establish support groups
  - To run workshops for carers and social events for children and carers
  - Run an online and telephone support forum
  - Employ support workers, engagement workers and advocates and policy advisers.
- Reach out to other groups affected by teratogen exposure
- To create **centres of Medical Excellence** to care for those affected by FVS and other teratogens; and provide support for the wider family unit.
- To ensure that a **Research Strategy** is designed which can assist those affected. Results of research should simply be used to provide information not just about the drug side effects but a system should be found which ensures that all possible impacts are explored and shared if required
- **To Design a Mechanism** by which families can be identified and warned, and given immediate early intervention to prevent adverse effects of one condition - e.g. low vitamin D and arthritis or dental problems, creating another.
- To enable **schemes which ensure reliable dissemination of factual information** provided by experts working alongside patient groups. This is particularly important when dealing with a clinical condition with so many 'unknowns'.

- To support charities and peer support groups to communicate and share with each other
- To assist those affected to reduce isolation.

OACS Charity notes from its experience with the Valproate Stakeholder Network that the success and quality of any future dialogue with regulators and other stakeholders is likely to be rooted in the good structural design of that dialogue, including:

- Even representation of the main groups affected
- Administration by trained engagement officers
- Consistent and skilful chairing
- Encourages discussion between groups with sometimes competing vested interests
- Identifies practical goals
- Does not seek to apportion blame
- Allows exploration of theoretical ideas that may go against the grain
- Allows enough time for culture change to develop
- Ensures the forum is a safe place for those with a lot to lose by guaranteeing confidentiality from publicity and media but allowing enough transparency with the group to break barriers and allow relaxed and constructive discussion.

**Finally, as those who have assisted in the preparation of this submission can attest, the campaigners and individuals represented by OACS Charity and FACSaware are highly experienced, hugely knowledgeable and ready to engage.**

## Conclusion

In this submission we have attempted to outline the 40 year history of FVS in the UK, not only from a regulatory and legal perspective, but also from the perspective of those for whom FVS is a day-to-day reality and not just a catalogue of legal and regulatory failings. In doing so, we have sought to inform the Review of the urgent need for compensation for all those affected by FVS, the need for disability services in the community to receive ring fenced funding to enable them to continue to provide the essential services those with FVS and their families need, and the urgent need for an overhaul of the way in which medicinal products (devices and drugs) are regulated in the UK.

In our submission, the history and present day reality of FVS in the UK provides the Review with a unique case study that exposes the long-term and persistent regulatory and legal failings that have not only created the tragic legacy of FVS but have left those affected unheard and uncompensated for far too long.

One day we hope we can get the justice they deserve and a future that will be secure and not full of uncertainty.

We note that upon announcing the current Review, the Secretary of State identified the need for transparency and action:

*“how [do] we regain the trust of families deeply scarred by these issues. He went on to say that: ‘We can do it in two ways: first, by being open and transparent in everything we do in this process so that they can see we want to get to the bottom of it as much as they do; and secondly by recognising the fundamental issue that in the past when we have assessed these clinical medical safety issues the voice of patients has not been as strong as it should have been. We have to put that right.’”*

It is submitted that by ordering a thoroughgoing Public Inquiry into the way in which medicinal products (both devices and medicines) are regulated within the UK: the way in which patients' voices are heard within that context; and the way in which patients can seek redress when they are injured as a result of products cleared for use in the UK, this Government has a real opportunity to achieve that transparency. By giving serious consideration to the institution of a Compensation Scheme for all those affected by FVS in the UK, the Government would not only be drawing a line under the inaction of previous administrations but would also be converting fine sentiment into real moral action.

As we move into a post-Brexit reality, this Government has a historic and unique opportunity to create a new regulatory framework for all medicinal products (devices and drugs) predicated on the precautionary principle and mandating candour in risk-warning by manufacturers and regulators towards patients and their treating clinicians.

In our submission it is crucial that the Government seize that opportunity by ordering a Public Inquiry and considering a Compensation Fund for FVS victims. In doing so Mr Hunt and his Government have a real chance to '*put it right*' both systemically for the future and historically for all those who suffer the day-to-day reality of FVS.

**These considerations are respectfully entrusted to Baroness Cumberlege on behalf of OACS Charity, FACSaware, and all of the victims and families that they represent.**

## **Appendices**

*These are provided in a separate bundle for ease of reference.*

## APPENDICES

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## APPENDIX A: Real Lives – Real People

### Case study 1:

My name is X, I am 46 years old, I have 4 Children. I developed epilepsy at the age of 12 years old. I tried several medications before being prescribed Epilim, which I was on until my youngest daughter, who's now 16 years old.

I suffer from Grand Mal seizures, I was not told that the Epilim would harm my children.

When I became pregnant with my first 2 Children, JSC (aged 29) and JC (aged 27) I was not seen by a Neurologist or GP only an antenatal nurse.

JC has bowel problems and has problems digesting food, sleep apnoea, panic attacks, hiatus hernia and reflux. His development in school was very hard; he has dyslexia and struggled right the way through school leaving without any qualifications. JC in his early years also attended speech therapy.

JSC has now developed degenerating disks and because of this she's had to give up work and come back home to the family so that we can all take care of her. She got 3 collapsed disks hitting her nerves.

BC was born with Spina Bifida, Hydrocephalus, Scoliosis, paralysed in her Lower Limbs, Partially Sighted, Multiple types of Epilepsy, Autistic, Downs Syndrome, Brain Damaged, Reflux, her organs are all squashed up in her rib cage, has no bowel movement and I need to evacuate her bowels for her, B's feet haven't fully developed. B has so many things wrong with her that I haven't even listed. B has a cognitive age of a 3-year-old, is in nappies and is non-verbal, she communicates with her eyes and limited hand movements and she is bed bound.

CC my youngest daughter aged 16 when she was younger she suffered very bad with her bowels and bladder, CC had to wear nappies to bed at the age of 14. She suffers very bad with her ears and complains of constant headaches and joint problems and has been under Chelsea and Westminster Hospital, they were hoping that she would grow out of them but hasn't.

All my children were diagnosed by Dr Peter Turnpenny with Fetal Valproate Syndrome when they were younger.

Since my first born I have had a constant battle with my children because of Valproate, visiting hospital appointments thousands of times and the amount of surgeries is more than a person in a whole lifetime.

I love each and every one of my children, but I have had to put my life on hold living day to day. Just this year began with my daughter BC read her last rights because she nearly lost her life. This is not the first time that I have very nearly lost her like this. Only yesterday I have been told that BC needs to have every tooth taken out.

I can not begin to explain how I feel right now, I can only exist day by day, I have no faith in Social Services, Health Care or Education, as a family we had had to fight for everything and I am still fighting for our rights. I am in mourning for my daughter BC, I have paid for her funeral and she's got a burial plot because when the time comes when she passes away I will not be able to cope. Day by day I am also watching all my other children go downhill. In one month as a family we have been to 25 hospital and doctors' appointments this is a good month. What I want from this is firstly all my children to be seen privately to have a full assessment to be able to see all their needs, and a promise to ensure that we all have the benefits that we are entitled to without fighting for it. My daughter BC is dying, and the council are taking rent from her and they have stopped my DLA

Secondly if I die I want to ensure that all my children have a home the care they need and enough money to have the life that's been taken away from them all. Someone must take responsibility for what has happened we shouldn't have to wait a day longer for the compensation all our families are entitled to for the damage it's done to my family and all the other families impacted by Valproate.

### **Case study 2:**

Epilepsy became a part of my life when I was born; I had not been given enough oxygen. I died a few times and this caused some brain damage. The human body is amazing; it healed by re-routing the neural pathways so that I was seemingly okay.

After my first epileptic fit I was put on sodium valproate when I was about 14. At the time the doctors were desperate to get me off it. I spent one term in hospital, this process continued when I finished my education and I spent another six months in hospital, and it was found that at that time I was only able to tolerate sodium valproate.

Until 1995 all I had been told; too many times, any children would have a 10% - 12% likelihood of having Spina bifida, and I was encouraged not to be concerned.

It is terrifying to have an epileptic fit. To feel your body be so completely out of control. Experiencing life threatening situations and the painful recovery afterwards. My epilepsy has never been in full control so the fear of changing medication after trying so many times in hospital, left me terrified. I guess it might have been with some relief that I was told that it was unlikely that I would have a child affected.

My first two babies were born early and classed as neo-natal deaths; I held them in my arms as they died; even today I know that there is no pain likes this sort of experience. After their autopsies I was told that they were too badly damaged to have survived, even if they had been born at term. I later had a late miscarriage; again I was told that she also would also have been too disabled to survive at full term. I now know that this sort of experience is not uncommon.

Both my girls were born in the mid-nineties. They are both so perfect, and I love them so much. My eldest is disabled in very different ways to her sister. She was born with two holes in the heart; Her APGAR was 5/10, she had jaundice, When she was little a weak oesophagus meant that she was sick so many times a day I had to carry a bowl around with me. Diagnoses of learning difficulties, autistic spectrum disorder, communication problems, hypertonia, physical malformations, club foot, neuralgia, and asthma. The secondary effects of the drug have meant that she has had 10 ops on her ears. She has chronic bi-lateral cholesteatoma with complications, this will be an issue she will have all her life. Tuille phenomenon (causes nausea, dizziness, echoing etc.), she is now very hard of hearing, hyperacusis, tinnitus is also problems that she lives with. She is a self-taught lip reader and does BSL. Because of epilepsy I had difficulty with BSL so I sign to her and she talks to me, when she is not using her hearing aid. I also trained as a lip speaker, and managed to get on what was the only level two deaf awareness course in the UK that year; this really helped me to understand her world.

Her younger sister has a milder form of Asperger's and has developed coping techniques, but in an unfamiliar situation and she falls into a major panic. She has poor muscle tone, and the classic FVS dysmorphic facial features. She was born with a number of cysts on her brain, and a cranial malformation at the top of her spine, just slightly too small to paralyze her. She has to wear splints – both leg and foot, as well as do exercises daily. She has a form of benign tumor that has once been operated on, on her foot. Like many of the children she has mental health problems. She also lives with chronic migraine, her digestive tract is weakened, she blanks out for large blocks of time, despite all of this she is doing level three health and social care: Level three supporting individuals with learning difficulties. She also volunteers as a helper at a local inclusive theatre project, volunteers for a scout group, attends St Johns Ambulance and is the youth representative of OACS and a trustee, giving a voice to the children within OACS, a role which has given us parents many insights.

I have since learnt that if you have one child effected you have a 55% likelihood of having others. I am lucky that I only care for two children; there are those that care for families with a number of disabled children. The strain can be too much for a relationship, my husband left me when I was pregnant with my eldest daughter, losing three children and facing a fourth is a difficult fear to live with. It probably did not help that I spent this pregnancy in hospital

### **Case Study 3:**

*A piece written for Baroness Cumberlege's Review from a young person affected by FVS:*

My mother was taking 5000mg of sodium valproate a day when she had me. I am only 22, but even I know that a number of doctors have chosen to write a prescription for sodium valproate at 5000mg a day and not questioned it.

When we were young me and my sister were going through a box in mum's room. We found some photos of little babies, mum cried when she saw us with those pictures she had hidden from us, that was when I found out about my sister Trelissa and my brother Keverne, they are buried in Bristol.

My mum was taking 3000mg a day when she had my brother and sister, my brother's kidneys were not okay, and my sisters heart was not okay so they only lived a short time.

I am writing this knowing that other doctors added on another 2000mg of sodium valproate and expected mum to have healthy kids!!!

I really do want to know; how could so many doctors let this happen?

### **Case Study 4:**

I had my first seizure at twelve years of age and my second seizure at 14 then was put on carbamazepine my seizures were not controlled all through school.

At 16 in 1996 I found myself pregnant due to interactions with medication and contraceptive pills. I had seizures all through my son's pregnancy then after he was born the neurologist slowly moved me to sodium valproate. I continued to have seizures off and on once or twice a year that were triggered by stress.

1999 I met my ex-husband and found myself going through domestic violence with physical and psychological abuse. In December 2001 I married him and was given strict instruction that he wanted a son so I had to get pregnant.

2002 I had appointments with 2 local GP's and a neurologist who assured us that it was safe to start trying for a baby and to remove my contraceptive implant; the only warning was spina bifida and down syndrome.

When I found out I was pregnant the doctor booked me in for a scan, at the scan I was told I was 8 weeks pregnant and I had twins; myself and my husband at the time were delighted.

At 9 weeks pregnant even though my husband had not hit me during pregnancy I left him and moved in with dad.

At my second scan I was told that I had lost the twin and this can be a normal; I was told the twin died at 13 weeks.

I had several scans during pregnancy to check for spina bifida and at 32 weeks they noticed the baby stopped growing and agreed to induce me at 37 weeks

### **Birth of F**

At the birth I was in complete shock I had trusted the knowledge and information the doctors had given me before conception and during the pregnancy and expected a perfectly healthy child.

The baby was born with an extra digit, hole in the heart and cleft palate. I invited my ex-husband to meet his child; once he saw her and I told him of her disabilities he denied that she was his as he could never produce a child like that.

The consultant at the hospital had said to me she thought that this was sodium valproate syndrome and sent genetics tests and consulted a geneticist to get confirmation.

I spent a month caring for F in the special care baby unit living there giving 2 hour feeds through a nasogastric tube the nurses had to teach me how to draw the stomach acid up feed her through the tube and wash the tube through with water. F started fitting after birth and after a CT and EEG was prescribed 25mg of sodium valproate to help with the withdrawal of the drug.

I was so exhausted during 2 hourly feeds that I developed an infection fever and continuous bleeding I was given antibiotics and told they would do the next feed so I could get some sleep but was back to the 2 hour feeds within 3 hours.

When I got home I still had her on 2 hourly feeds continuing the tube feeds while being a mum to my 7 year old son. F would pull her tube out regularly and sometimes twice; a day a community nurse would come out to put another one down so she could eat.

With the hole in the heart F was prone to catching chest infections and was in the children's ward on a monthly bases spending days sometimes weeks in there.

My epilepsy started to become a problem with no sleep juggling a 7 year old and a baby that needed fulltime care I was monitored by my doctor and told to try sleeping. I started to feel isolated and confined to the house as I could not drive and there was no nursery or baby group I could take her to that would include anyone going through what I was.

The sight of a perfect baby and their parents talking about how their child's first smile came - always made in cry inside.

At 1 1/2 years old F had her first operation the cleft palate repaired:

I was not prepared for the long wait while in surgery and then the doctor coming to me saying she was in intensive care unable to breath on her own. F spent two weeks not breathing on her own, asleep. I stayed in a hospital miles away from home; it took an hour for my dad to drive my son to see me for a few hours a few times a week.

As I walked into the room she had tubes in her mouth her veins had closed off and the only vein they could use was a one in her head. There was blood coming out of her mouth and nose. I was traumatised by what I saw as nobody prepared me for what I would see.

When F got home she was followed up by 6 monthly reviews of the cleft palate where they would bring nurses, photographers and psychologists, these reviews still continue today.

In these reviews I felt angry and upset that they sat a psychologist with me and asked me how I was feeling, when I asked why a psychologist was here she said that some people blame themselves for their child's cleft palate my answer was clear "no it's not my fault I asked the right questions and got the wrong information I don't blame myself".

F's second operation was not until she had got bigger at 4; this was for her extra digit removal and extra joint in thumb removed in right hand. For this the aftercare was hard she wore a metal splint with pins going through her hand to keep her bone in place while they healed and

then another operation to take the pins out once healed 6 monthly reviews also. Then her other hand had to be down a year later extra joint removal of left hand and webbing increase. When F was 6 I got my first word out of her which was choc, she wanted chocolate.

F had appointments at the craniofacial clinic in Birmingham because her fontanel was closed at birth, the doctors were worried that she may not have space for her brain to grow and wanted to have regular MRI scans. This was another horrible experience; the doctor telling me they may need to break open her skull to let her brain grow no mother wants to hear that. But luckily this did not happen.

Through the multiple operations hand surgeries, leg, surgery's pins in her hips due to dislocation and not walking unaided until about nine.

At home I had to do physiotherapy for F, after care with all operations and re-bandage her splints; so I was also her nurse too.

When F got to about 7 I noticed a noise sensitivity which I asked for help from her paediatric consultant at this time F had a special wheelchair that sported her spine which allowed me to take her on the bus. F's tantrums started with head banging and self-harming and throwing things. The doctor suggested whining her into the nose.

Later on at the next appointment the paediatric consultant had suggested that I let F go to respite care on a weekend, it took me some time to trust another person with F but the doctor said that she had a patient that lived with his parents up until they died they placed him in a home after this and as he had never learnt to cope without them, he took a nervous breakdown and ended up in a home for mentally disabled. So, I agreed to the respite.

### **Building a future for me and my children**

In 2010 the group litigation collapsed I did a story for my local paper titled all I want for Christmas is legal aid.

With no hope from the litigation I knew I need to protect my daughter and her future, so as her hospital operations had settled down I decided I needed to go to university so I repeated my GCSE'S in night class and because of my anger and frustration that the evidence was there but nobody cared enough, it pushed me towards evidence and took a forensic diploma course which I found that I loved.

I then went to the job centre to tell them of my plans to go to university to do forensic science, they told me "not to bother just stay on the benefits".

I knew I wanted to make a difference in the world I wanted to help people get the truth.

In 2012 I started a 3 year course at the university of Cumbria, however being a fulltime student meant losing my income support and had to go through student loans company I soon realized that there were grant available for students that were carers looking after parents but nothing for a parent caring for a disabled child, I was angry and felt discriminated against because I was a carer. I got the same support and money a single parent would get if they went to university.

I loved university I felt like I had a purpose and that and that I found me again my own life separate to F take was not about F it was for me.

While at university I was a carer from 7 in the morning to get faith ready for school and feed her wait for my dad to come wait with her and set off for university at 8am to drive for 1 hour to get to my university for 9.30 to have me first lecture at 10am, then finishing university at 5pm sometimes 4pm 1 hour to get home put my carers hat back on until bedtime for her then start onto assignments and coursework.

In 2<sup>nd</sup> year 2013 F had another operation on her tongue and teeth removed and the next day straight back to university. I also arranged my wedding and reception alone as my husband was always away on deployment in the navy.

3<sup>rd</sup> year of university I met peter white from crime scene to court author and he thought I would go far as he thought I was a determined person.

I told him about my role as a carer and that at the start on the year I got the flu and still passed my exams even though I lost my voice, I continued to tell him I caught the chicken pox for the first time in my life and was banned from class for a week and then 3 of my discs slipped and I was in constant pain.

I got told by my doctor that because faith had to be picked up so often after tantrums, picking up the wheelchair and long nights till 3am some days working on my computer had damaged my back.

To get through lessons I had to lay on the back table listening and watching lectures as I did not want to miss anything.

### **The challenges I face being an epileptic mother:**

Epileptic seizures can be triggered by many different things depending of the type. Stress is a common trigger that increases the risk of an epileptic seizure looking after a FACS child is increasingly stressful, for example continuous battles with SEN services and local authorities, continuously explaining sodium valproate syndrome to professionals and teachers, other parents staring at your child because of constant tantrums in public places. The frustration of nobody listening to your opinion at school because they are the professionals you're just the mother. I am now fit free since 2009 and have a full driving licence however if I have a headache or feel tired I won't drive just in case I could have a seizure.

The frustration and stress battling to find myself within F's world, at some point it all became about F I got lost somewhere, my dreams got lost, the more I fight for something that is just for me the more I lose the fight.

### **What are my concerns for the future?**

As F gets older I worry and fear for her future; examples why:

My child is going to be a vulnerable adult and only has the mental age of a 3 year old, she has no sense of danger, no stranger danger no road sense and she wants everyone to be her friend.

In the papers recently and in the media it has been concerning of the amount of abuse directed at disabled people.

FACS children have a hidden disability it worries me that they are so vulnerable to predators and people that would take advantage of that vulnerability.

Housing is going to be a problem; placing a vulnerable adult in a location that is safe would not be possible if left up to the council, especially with the cuts being made; she would end up living in a bad area.

My children as well as many others will not be capable of living a life independently without constant supervision.

My child does nothing for herself and whilst doing research on residential schools I found the parents agreeing that their child had progressed and become more independent away from home this is an option I think is needed for FACS children.

The schools and SEN don't understand the needs of FACS children and a plan written for educating FACS children so that SEN are not bound by funding and criteria fitting: For example my child has autistic traits autism is known to get worse as a child gets older however my child is still 3 to years of age so her autism can't be diagnosed fully and unable to attend schools for autistic children.

### **Case study 5:**

When my daughter was born I knew there was a problem but my concerns were ignored and I was discharged from hospital despite a young nurse bringing in a paediatrician to speak to me. He dismissed her and me. Eventually when my daughter was 6 months old she was referred to a paediatrician by the GP who diagnosed her with developmental delay. She was referred onto a clinic where she saw a different paediatrician, occupational therapist and educational psychologist. She saw them every 6 months until she started school at 5. She attended a nursery from the ages of 3 to 5 which was specially set up for toddlers with different forms of difficulties and it was excellent. At the age of 4 my daughter was statemented and I had to appeal the statement because it was completely wrong. The young girl who assessed my daughter was excellent but her report was edited by an educational psychologist who had never met my daughter. They wanted to send her to main stream school and I fought that decision and won. At this point we did not know what had caused her developmental delay. School was difficult because no one understood my daughters' problems especially the anxiety. She was incredibly unhappy at school.

My daughter was diagnosed with FVS when she was 16 years old. It was too late for the diagnosis to have any impression on her education. We were lucky enough to get her into a special needs college which helped her immensely. The psychiatrist who headed this college showed a special interest in my daughter as he had never heard of FVS. She was able to attend this college for 3 years but it was a fight to get the funding with no support from anyone.

In fact the support that was offered hindered the progress of the application. My daughter had to move away from home to Wheelsby College in Grimsby in order to access this kind of college setting as there was nothing locally apart from the mainstream college where on a day visit she had an extremely bad experience.

After college we found a residential home in Bexhill which worked very well for a few years. Every year she was assessed by social services and we went through the anxiety of not knowing if the funding would continue. Eventually the home was sold to another company (after all it is a business) who changed the dynamics moving in more severely disabled adults leaving my daughter out in the cold because she is more able bodied.

We searched for a new home which took us all over interviewing managers and viewing the homes. We found a home in Witham which is where she is now. We still have to go through the anxiety of yearly reviews knowing the funding isn't sufficient and that we will probably lose the battle to have it increased.

My daughter struggles every day with tasks that are second nature to us. For example, asking for assistance in a shop, not being understood and having someone else translate for her. She has learning difficulties, immature speech, autism, dyspraxia, curved spine, poor fine and gross motor skills and cannot read or write. She is 32 years old now and living in the residential accommodation with 3 other adults of similar ability. The current cost of this is £1011.08 per week and is funded by social services. My daughter contributes £340.00 a month from the benefit she receives from DWP. In addition to this we pay a premium for the use of the car of around £40 a month on her behalf (which she would be paying if we didn't) leaving her very little money for necessities such as clothes, shampoo and soap etc. which is not covered in the cost of her placement. The £1011.08 is to cover the cost of her room, carers to be present and 1-1 care for 2 hours a day (which is not enough). There are carers present on the property 24hrs but there is no wake night for my daughter only a sleep in for her and 2 others. The 2hr 1-1 funding is supposed to cover assistance with washing dressing, tidying her room, washing, drying and ironing her clothes, teaching her to cook and develop independent skills. It is also to take her to hospital appointments if we are unable to take her. I could go on but as you can see the amount of time allocated is insufficient. This level of care provided was inadequate at the beginning but since then she has developed epilepsy and the level of care has not been increased despite the fact that her needs have changed dramatically. It is an on-going battle trying to ensure our daughter has the right support. I have sent countless emails and made numerous phone calls asking for an increase in her level of care to no avail. It was only when I raised it as a safeguarding issue that social services took action. Their action was to arrange an appointment for a review but not until my daughter had been assessed by a neurologist. The fact that her symptoms and vulnerability are there whether or not she has been seen by a neurologist has been ignored. It just drags on. This is a prime example of the issues an adult with FVS can face.

Then there is the issue of claiming benefits. It is more than obvious that my daughter cannot work. She lives in a residential home with continuous supervision. You would think the fact that she has 24 hour supervision shows she cannot be self-sufficient but I still have to reclaim her support allowance every 3 years. I understand that this is now the law but why would an assessor put her into the return to work support allowance TWICE. She had to go to an interview at the jobcentre in order to continue receiving her benefit (which I took her to as she couldn't attend on her own) while an appeal was being processed. If I was not doing this for her who would? She certainly cannot do it herself.

I can honestly say from my experience of 32 years there has never been enough support/facilities within the community to cover the needs of my daughter or any other person with learning difficulties/special needs or disabilities. To add to this there has been a continuous lack of understanding of the complexities of FVS.

### **Case study 6**

The challenges of raising a child with autism are great but with the right help and intervention many of the negative behaviours', such as tantrums (meltdowns), difficulties in communication and socialising, educational needs, etc., can be mitigated to some extent. However, if the child is also diagnosed with FVS a whole host of other problems come into play. The most obvious challenge is that the FVS child with autism looks different physically and parents have to deal with ways their child is perceived by others who do not understand the difficulties that are experienced on a daily basis. However the real challenges are having to deal with other FVS symptoms which need intervention not associated with autistic behaviours.

How do you explain a medical procedure to a person with FVS and autism when they can perhaps only understand two words in a full sentence? How do you prepare a child for a stay in hospital that needs constant routine in their lives to avoid the severe anxiety or fear that this causes to a person with autism? There isn't an easy answer but education and information helps. When my 16 year old son fell at nursery school (aged 3) and split his lip this involved a trip to hospital where he needed me to be with him to keep him calm. I was very impressed when a nurse, who was expecting us and clearly understood autism, greeted us at the hospital entrance and took us straight to a lift. She immediately told the very large queue of people that the lift was unavailable to them and asked them to move before escorting my son and myself into the lift and up to the children's ward where we were given a quiet room with LOTS of toys to keep my son occupied. He needed a general anaesthetic for just three stitches!

Never underestimate how good this treatment was. If I had had to take my son into a crowded hospital entrance and lift he would have likely had a major meltdown which would have involved him banging his head on the floor, biting me on my hands and arms and generally throwing himself wildly at me. Fortunately I am fairly good humoured and able to distance myself from this behaviour by just sitting quietly until it subsides. But if he had done this with his split lip (which was bleeding badly - though he didn't really notice it) then he could have made it much worse. At three, my son had no speech at all - he would take my hand and lead me to the fridge if he wanted a drink - and he would not engage in any eye contact. Explaining the situation was impossible. The only thing I could do was to play with him and keep him as calm as possible. I was his 'routine' - his comfort blanket.

After his surgery, which I had been told was only going to be about half an hour, I waited in the corridor. Two hours later I was beginning to panic - a lot! Nobody had told me that he was in the side recovery room. Being a mum I was imagining the worst. The corridor was so quiet and remote and there didn't seem to be any staff around. Then suddenly a trolley was pushed past and a small boy sat bolt upright and shouted "Mummy!" to me. The relief was unbelievable. More surprising was the fact he had called me Mummy for the first time. I didn't hear that again for another three years... (An important lesson - he could understand more than he could communicate and he DID recognise me)

I knew that my son looked different to the other children with autism and this was confirmed when I went to an autism conference in 2001. I was attending in my professional capacity as a psychology lecturer and my son's nursery teacher was also attending to find out about autism as my son was in her mainstream class and she wanted to find out more about his needs. During the conference there was a lecture about the apparent rise in autism and some physical features were described that were different from previously diagnosed cases of autism. The professional team who were dealing with my son then called me over and said they had been discussing him as he seemed to 'fit the bill' with his unusual eyes and other features. No mention was made of FVS at that time and I certainly wasn't aware of it then.

Bringing up a child on the ASD is a huge challenge in itself - add the complications of FVS to this may explain why the child has difficulties but it doesn't change anything. The child may change as they grow older, and if they get good early behavioural intervention, speech therapy where appropriate, education suitable to their specific needs, then things can become a little easier. I would describe my experience of with my son as much easier in some ways now (fewer tantrums and better attempts to communicate/instigate communication) but more difficult in others (cannot go out on his own/ make friends/ limited independence).

We have learnt to manage his tantrums or intervene to prevent them occurring. We can successfully take him out for a meal with us and he will behave impeccably and is polite to everybody and will order his own dinner. Conversation, however, is virtually nil. We can attempt to engage him in conversation but in reality my husband and I simply end up talking to each other while my son sits quietly eating his meal. (He is surprisingly good and will eat most things and enjoys trying out new foods) This is something we could not have contemplated a few years ago as we could not predict how he would behave and so would be on tenterhooks all the time - not exactly enjoyable!

At 16 my son attends an 'Into Work' course -far too optimistic but his special needs school recommended him. He has to have a taxi to pick him up and bring him home. He is not allowed to leave the college grounds as he is unable to recognize dangers and cannot cross a road by himself. He also doesn't understand that a moving car on a driveway is just as

dangerous as a moving car on a road. We have tried consistently to teach him but with no success at all. If we ask him to look out for moving cars he is unable to distinguish a moving or stationary car.

At college he was given an email address but he has never accessed it and doesn't know what email is or what to do with it. We had applied for an Educational Maintenance Grant for him but heard nothing. When I contacted them to find out what was happening it appeared they needed more information from me - which had been sent to my son's email address... I am his financial appointee because he is unable to deal with any form of correspondence or financial affairs. They have had to change his email details so it all comes directly to me now.

Despite his difficulties he has made some lovely things at college including a wooden bi-plane and a superb moulded chess set with a chess board (we don't know how much help he was given as he can communicate very little of his college day) and he has clearly enjoyed being there.

A lot is made about encouraging independence as they get older - and of course all children should be encouraged to achieve their potential. However I also wish that professionals would understand that parents/carers are probably best at recognising their children's difficulties and limitations and not simply assume that 'we are frightened to let go'. We have encouraged my son to do all sorts of activities such as swimming, riding, playing musical instruments - he even went to Glasgow to swim in the Scottish National finals which involved a couple of days away with teachers from his special school, and he used to go to a respite bungalow once a month. Personally it didn't make any difference to us as we normally take my son with us when we go out but I would recommend respite to families where there are similar age siblings so they can have a dedicated night with parents/caregivers without interruptions.

We are presently doing up two rooms at the end of our house so that he can have a 'bedsit' arrangement and feel a bit more independent while getting the attention and supervision he still needs. He can have a fridge for snacks, possibly a kettle to make himself hot drinks, etc., but he will still need to join us for a family meal as he cannot cook a full meal. Without supervision he would eat poorly and probably eat all his food in a day or two and go without because he has no concept of managing his snacks anymore no more than he can manage his financial affairs.

Also it is important that we encourage him to keep touching base by coming out of 'his space' or he could go for days without any interaction. He would like friends but he has no idea how to go about achieving this. When pressed he will describe a couple of lads he is at college with as 'friends' but when observed there is little talking or interaction. He is also desperate for a girlfriend but does not really understand the concept. That has its own problems. The reality is

our friends and his brothers, who live away, are his friends by default. This doesn't seem to bother him and he enjoys it when we have visitors. Of course we worry about his future when we are no longer here but we do not envisage him living away from us as he simply would not understand why he cannot be with us. Equally we cannot imagine a life without him in it.

The sudden drop off of services at 16 when they are deemed an adult can be alarming and happens in a relatively short space of time. We are dreading the next step - leaving college. There is no way that he would be able to hold down employment. He has the communication skills of a 6/7 year old and would need constant supervision and attention. It is difficult to imagine any form of employment where this sort of support can be achieved. The problem we can envisage is that he appears much more able than he actually is - this is a real problem as if he has to attend a work capability assessment he would likely answer that he can do things just to please the interviewer. Obviously we will have to apply on his behalf for benefits to cover the loss to our income - the most obvious one being Child Tax Credits and Child Benefit which we can still receive while he is in full time education - but we do not envisage a smooth transition.

In conclusion it is really difficult to fully appreciate the extra challenges of autism in a child with FVS as there are clearly many and often it is difficult to distinguish when the difficulties are due to FVS or the autism symptoms alone. The reality is that the challenges of a child with complex needs are many and a holistic approach via a multi-disciplinary team involving parent/caregivers and professionals is essential but services may be patchy nationwide. The parent is often left to find out what is available for their child and may have to fight to achieve a service or intervention. I think my professional background meant that I was able to access services and a diagnosis much sooner as I recognised the developmental problems before my son was two. Also I tend to be fairly proactive in finding out what is and what isn't available. I wish I had been better prepared for certain transitions such as educational changes, etc. There is a tendency for educational and social work professionals to try and shoehorn your child into services that are available rather than try to provide services that are actually needed. Also I wish I had understood much sooner that the services that are available are often dictated by current policy and ideology which may or may not suit your child or your families circumstances. The one thing I learned is that you are your child's best advocate and that is a skill that has to be acquired very quickly!<sup>1</sup>

#### **Case study 7:**

X has FACS and has moderate learning difficulty and will always need support with her literacy and numeracy skills which will severely restrict her day to day independence any future job prospects.

X's engagement in completing ordinary day to day tasks is also restricted by her FACS. X is unable to attend shops and banks independently and is unable to budget. Specific support has been given by social services to X to support her in accessing banks, post offices and shops and her family have to include X in the weekly shop to try and develop her independent living skills for the future. X is currently evaluating with the people who support whether she can live independently in a supported unit.

X's syndrome manifests itself in a number of ways and as such has affected her development and her ability to live independently of 24 hour support. Though support services are of the opinion that she has the potential to develop skills to be able to live with a lower level of support in the future and she has completed an employability course. However, the distances that she is able to travel independently will severely restrict the employment opportunities available to her. Further X requires significant structure and organisation for her day to function which too will need to be considered at the time she gets a job. Other factors that X will face when it comes to her employability is that she struggles with personal hygiene, has to manage her behaviour by keeping away from situations that agonise her and has a tendency to blame others when she forgets things.

### Case study 8: costs of care for one individual with FVS

Costs to Social Services for child X when X is an adult assuming X lives to 70 = £5,257,000.

Description	Per week cost	Per year cost	Cost for 50 years / or to date
Accommodation, personal care, day care recreation and outside supervision	£2,000.00	£104,000.00	£5,200,00.00
Social worker – salary £30,000.00 which is £40,000 – to the employer	n/a	£1153.00 (£40k /52 weeks/40 hours x 60 hours)	£57,692.00
Cost to Local Authority Special Educational Needs department [initial statement, subsequent statements 9 plus 7 anticipated future statements; 1 -1 support worker; cost to the learning autism support team; educational psychologist past and future; special school placement; transport to school	n/a	n/a	£317,000.
Cost to date to University Hospitals Consultant paediatrician;	n/a	n/a	£3937

Physiotherapist; Ophthalmologist; Clinical Geneticist			
Costs to date to a Primary Care Trust	n/a	n/a	£3026
Audiology; speech and language therapy; travel costs; (autism diagnosis team costs are unavailable)			
Cost of welfare benefits paid to mum	n/a	n/a	£100,000 <sup>1</sup> (approximate)
Income support; ancillary benefit such as free prescriptions and council tax benefit; free school meals; disability living allowance; carers allowance			
Legal Aid funding for litigation against Sanofii Aventis	n/a	n/a	3.25 million <sup>1</sup>
Costs to other organisations	n/a	n/a	n/a
Preschool placement; play schemes; glasses; Red Cross funded 1-1 play schemes; Sikh community play scheme;			
Cost to welfare department to be determined at a future point in time	n/a	n/a	n/a

**Case Study 9:** *A letter written to those responsible for this submission by one young person diagnosed with FVS:*

Hello,

I am X. I'm autistic, anxious, and an overall "interesting" person. I've been told you're interested in knowing my anxieties, worries, and what I feel would help and is important. I'd like to preface this by saying that this is only my own perspective, and that different people on the spectrum are different.

Firstly, what worries me – I find that the future is something that always causes concern for me in multiple aspects. Due to the nature of finance and its importance to being able to live, I worry about the ability for myself to make money in the future. This probably sounds greedy or perhaps obscene as a concern, however it's less about luxury and more about being able to survive in a world where everything costs money – to the point that perhaps one day breathing may have a price tag. This is a concern of mine because I find myself unsure of my own ability to work. What if I have an anxiety attack at work? What if I try to go into self-employment but fail? What if I try to work for someone else, but it goes terribly? That last point is a fear of mine

that is only further emphasised by the statistics. Any research into the unemployment rates among autistic individuals never tended to give pleasing results. Yet, what does this mean? Does this mean I'll be among the minority of those that succeed in the employment department? Does that mean I succeed because I'm not as on the spectrum as I am? Does it mean that the majority of the failed success stories comes not from the fault of the person, but the mere presence of the label that holds more misconceptions than facts? These questions are the ones that tend to drive me to worry, and cause my stress to ever increase.

I also worry about the future as just a general thing outside of work and finance. Right now, I am not a very independent person. I'm discomforted by fire, scared of crowds, and as a result struggle with both cooking, and going out into the world alone. This, coupled with the fact that I do not know how to use items such as washing machines or dish washers, means that right now I have little independence. It's not something I like to think about, but what does this mean for me when I'm alone? When my family either moves away, or dies? They don't teach independence in schools, and if they did, nobody ever felt it an appropriate discussion in education to hold with me. It's just been something I've tried to work on with my parents.

And what about friends? Whether because of my diagnosis or because of the label that comes with it, I can have moments of feeling isolated. What do I do if people I become friends with die, or move away, or decide they don't want to be friends anymore? I do not know how to "make friends". Relationships such as that tend to be fickle and incomprehensible to uphold, with so many social rules and things of understanding that I have never fully been able to grasp. But does that mean it's something that I will need to learn? And if so how? Is there even support for something as vague as friendship? Or does it simply come down to a "knack", meaning that in the future when people move on, I'll be alone?

I hold so many questions inside my mind that I feel I would never have to think about and perhaps the answers would be second nature to me, if they had been addressed earlier in my life. I wish there were people to talk to me – to help me learn how to work around my problems, to accept who I am, to learn how to work, how to play, how to live. I've found a majority of the decisions in my life have occurred at the behest of someone who had only ever known me as a name and a number on a piece of paper. To be reduced to simple symbols. I recall one instance where, in a tribunal meeting, I had to work up as much courage as I could to tell of the story of my isolation to someone who viewed me as little more than that piece of paper. To get the support any of us need, we need to put our weaknesses on display, and inform those who would judge us that we are weak. We need to not only be able to confront our weakness, but in order to get any help, we have to publicly and shamefully declare our failings in body and mind.

It is devastating.

It is especially devastating when even after all this, when having bared your chest and your vulnerabilities for all to see, you are still denied help. You're just a little anti-social. You've just got a few anger issues. You've just got exam stress, everyone has it. To have to fight, and fight, and fight, just to be seen as someone worthy of treatment as a human being, and to be able to live your life like those peers among you without as many difficulties would. My

younger brother is one such person who this confrontation is too much for, as he puts on an affront and denies all that would point to his own shortcomings. Not because he thinks he doesn't have them, and not because he does not have them at all, but because it hurts. To tell people you don't trust – and rightfully have no reason to trust – every vulnerability of your person. And then, even when you have done so, to have your weaknesses seen as minimal, to be worked and drilled into by a scrutiny of the eye that seems to scratch at the surface of your sanity just because you're a name on a piece of paper, and help would cost money.

But where was my help when my daily school life was hiding in bathrooms, because my oddities were a cause of contention and bullying from both my fellow students, and in multiple instances, even members of the school staff itself? Where was my help when this initial bullying led me to develop further difficulties that did not exist prior to then, developing into anger issues that later developed into self harming issues. Was I merely faking a problem that was not there when I smashed my head into a flint wall? Or is it perhaps that our words are soundless to those who do not wish to hear them.

Honestly, I don't know. I doubt I will ever know. We only ever see our own perceptions of the world, and mine feels like it shifts between colourful, and bleak. At first, I imagine I would have been helped by having someone to talk to. I have people I talk to now, and it helps for sure, but I cannot help but find myself pondering what would have happened if my first anguishes for help were listened to by people that were not my parents. It's all well and good listening to the parents, but then it is claimed that it's in the interest of the parent, not the child. So, why is it the child never gets to speak? Is it because they're too young to be able to understand such a sensitive topic?

If such is the case, then I admit I would be curious to find out what the socially conceived age is where you have a discussion about how a child has neurological or physical (or both) difficulties, that there are things they will struggle at, things they'll be great at, and that their future is likely to be influenced by people they have never met before, and their need to save money. Because it's their "job" to ensure that funding is not mismanaged. So, of course, rather than learning every in depth story, and speaking to the people that struggle, it's just cheaper to deny them the help they need, which in some cases can be life saving.

When I first found out I was autistic, I was young enough that I only vaguely remember it. My mother would be able to tell you the time properly, since she remembers it more fondly than I. I asked why I was different, and my mum had been planning a full speech for when the inevitable day would come to broach the subject. I was distracted by butterflies, hence why I don't have great memory regarding the subject, but the fact of the matter is, it clearly stuck, because since that day I've known why I was "different". Was I too young to properly understand? Perhaps. But an answer that saves you as much confusion and loneliness as that sticks, even if you don't fully understand.

Which, I suppose, leads onto what I think is the most important thing for me personally.

Understanding. Or rather, trying to understand. It's impossible to fully comprehend the nature of a person. People are complex like that. Yet, to categorise people in a spectrum under a

singular label, and declare that those with said label all need the same “treatment”, is what I feel defines ignorance. A spectrum displays many colours, both vivid and dull, and these appear not only in the spectrum, but within every person that falls under it. We’re all colours, and to categorise us all as, say, blue, would be to take only a singular aspect of ourselves – one which some may have less of than others – and have that be what defines us. Why must I be defined by a label that exists to help me, if that label is the reason I am so ignored by the system that is designed to both aid and restrict me? Instead, I think it’s important to talk. Talk to the child, the adult, the parents, the staff of schools, the doctors. Don’t just get the outside perspective, and don’t just get the inside perspective. If you look for more than one colour, you’ll find the whole picture.

I guess that’s a bit ramble, and I apologise. I tend to find it easier to write things out that are hard for me to think about if I think about it in the sense of a story. So, consider this the story of my fears. I don’t know if this will help or provide the need it was intended for, as I’m afraid just thinking about my own weaknesses as a person, and my own anxieties of the fear, has made me somewhat forgetful of the initial purpose of this letter. Regardless, I hope it helps. Thank you for reading this somewhat aimless meander into my life.

Sincerely,

X

### **Case Study 9:**

The day my life changed:

It was the Easter holidays of 1983. I was out on my push bike, as I often was, and had been out around the village of Yapton and had just arrived at my aunt’s house. Even though it was 35 years ago, what happened next will remain etched in my memory forever.

I was chatting to my aunt in her kitchen when suddenly it felt like I had no control, my head wanted to turn to the right and there was nothing I could do to stop it. Then my vision started tunnelling, I could see my aunt but she was getting further away, I could hear her, but she couldn’t hear me. The next thing I knew I was coming to on the kitchen floor, and it felt like that was normal. I remember hearing my mum and aunt talking, having a cup of tea, I remember thinking that it was all normal, what happened every morning and my usual sleeping place was the kitchen floor. Also, I remember thinking that actually I was still tired and would go back to sleep for a while.....so I did!

That was when my journey really began, everything that happened before that moment felt like it had happened to someone else. I was lucky that my mum was a nurse at the local hospital so she remained calm and knew exactly what to do.....my mum and my dad became my rocks for the next few years.

The local doctor visited and I started having tests at the hospital, I would have to go to the King Edward private hospital at Midhurst, as St Richard's didn't have a scanner. I was having regular blood tests and EEG's done as well as the neurologist tried different medications in an attempt to control the seizures that had become a part of my everyday life. As the seizures took over my life, my confidence left me and I became more reclusive. I stopped doing my drama and sports, I no longer attended assembly and spent a large amount of time in the sick room at school. I was no longer able to ride my bike anymore, so could not get myself to the train station and to school independently. The trombone was no longer an instrument I could play anymore due to the increasing number of headaches I was getting, so I dropped out of the school band too. I became so invisible at school a lot of my friends thought I had left ( I found this out many years later when my paths crossed with one of these girls).

Looking back through old school reports, you could see a pattern (hindsight is a wonderful thing). My reports had said that I was lacking concentration and not listening in class and my marks had started to drop, that was when they identified that in fact I had been having petit mals for some months before my first grand mal. My seizures fluctuated as they tried different meds, I remember being particularly bad when they tried me on Tegretol. Eventually, they discovered that Epilim (Sodium Valproate) and Epanutin (Phenytoin) controlled my seizures. It took them two years to find the right balance that worked for me, so at that time, I thought Epilim was brilliant, it had given me my life back.....little did I know what a huge price my children were going to have to pay for that. It was not a trade I would have made if I had known. I would have rather risked the uncertainty of a seizure than risked my children's lives and futures.

My later years in school became a blur for me and I eventually dropped out as I was struggling more and more to concentrate and my careers teacher had told me I could never follow my dream of a career on the stage. Basically I gave up, I felt my life and my choices had been taken from me. I had no self-confidence anymore and my self-esteem had hit rock bottom. Certain teachers at the school had made me feel that I would not be able to have a career anymore, so I dreamed instead of meeting someone and having a family. That is when I met my first husband, Alan. He proposed after a week and I said yes! We had our first mortgage within months, I was seventeen. We got engaged officially on my 18<sup>th</sup> birthday, and married a few months later. In my mind, I had no reason to go slow, this was my future now.

When we decided that we would like to start a family, my mum and I went to see my GP so I could ask him about the risks associated with my medication. With my mum's medical knowledge she felt it was a question that needed asking. I was reassured that Epilim was the best medication to be on in pregnancy, and that there was a minimal risk of spina bifida (which could be scanned for during pregnancy) and cleft palate / hare lip (things that were correctable by surgery). This reassured me and I relaxed more as the scans revealed no problems. The pregnancy progressed as normal, although my original due date kept being moved back so it started on 23<sup>rd</sup> February, D was born on the 25<sup>th</sup> April. I remember thinking he was never going to make his appearance and so the night before I was due to be induced I unpacked my cases to repack the next day.....I awoke in labour so everything became a panic.

D was born in the early hours of the morning, it was a normal delivery but due to his size (he was 9lbs 11.5 ozs) I needed an episiotomy and stitches after. My mother arrived in the room just as my legs were in stirrups; she happened to be on duty that night and came across as soon as she received the news. I remember feeling huge relief that D was ok and that the meds had not caused any 'damage' as physically he was fine. In fact, he was a model baby, he would sleep all day and sleep all night. It was wonderful having a baby that always slept, but it meant he missed out on a lot too. He would sleep through a lot of toddler groups and playtimes. I remember I wanted to breast feed too but was told that due to my medication it would not be a good idea, so I followed that advice and bottle fed him. He started on solids at two weeks and grew at a fast rate, he was nearly two stone by the time he was walking at just under the age of 2 years. His speech was delayed so we were referred so that it could be monitored. His speech improved after he started nursery at the age of 3 and he started to talk more. I remember as a baby/ small child he was regularly under the doctor with repeated ear infections.

When trying for my second child I was given the same advice as the first time, that I would have regular scans but the risks were minimal. I was also told again to bottle feed so that there was not extended exposure to the medication. I went into labour early with J and had a very long labour. Despite the length of it, everything went well and she was born weighing 6lbs 15.5 ozs. I was so elated to have had a girl to go with my little boy that I didn't believe them when they first told me, I questioned them saying that they must be wrong and it was a boy.....they weren't and she wasn't! D adored having a baby sister and he was the perfect big brother. J like D slept through the night, almost from birth. I felt very lucky, my children had come through the pregnancy unscathed. They didn't have spina bifida, they didn't have a hare lip or a cleft pallet.....all was well.

As babies and toddlers, D and J were like the perfect models. They did as they were told and they rarely fought or kicked off. However, as they got older their anxieties grew. D was very clingy when he started nursery, and when it came to school I ended up having to drag him into the classroom to leave with the teacher each morning, as he didn't want to be there, he was struggling with the other kids and being bullied by one in particular. He was referred to see an educational psychologist at the age of 7 years.

J didn't want to go to nursery, she used to kick and scream and it used to break my heart every time I had to leave her. She had also developed severe asthma at a young age, this was further complicated when she contracted Whooping cough (I had been advised not to have them inoculated due to increased risks with me being epileptic, so as before I followed Drs orders). This made J very ill, she was constantly throwing up from the coughing and lost a lot of weight. Fortunately she avoided hospital but was in isolation for about 6 weeks. This left her with an underlying cough for several years and she was required to have the flu jab from a young age due to her respiratory problems. When we moved and they started at a different school/ nursery things seemed to improve where friendships were concerned. D and J remained each other's best friend and spent all their spare time together when they weren't at school.

I felt really guilty as a mum when I split from my first husband and I tore their world apart. Because of our difficulties I moved in with my brother 55 miles away, with the children. I settled them in the local school which was ideal with small classes and they thrived. Eventually I rented my own place and the three of us were quite settled for a while. Unfortunately, when my lease ran out I couldn't find another house and we were given no choice but to move back to my ex marital home. We settled back into our old home and the kids returned to the school they had left 9 months before. It was at this school, in the playground, that I met my second husband S, this was to be a source of irony as we were to later have lots of trouble there with our youngest children.

S and I lived between each other's houses with the kids, (D, J, and Steve's son S) and we used to go to the holiday and after school club that Steve chaired and volunteered at. Three months later I found out I was pregnant so a decision was made that we would all move into S's house I and would give up mine, I was devastated to lose my lovely house by the sea but we needed to be practical.

J struggled with the change and developed enuresis and despite, alarms, being woken in the night and other strategies nothing helped. This led to frequent trips to the Enuresis nurse until eventually it settled.

We deliberated over whether to continue with the pregnancy as it was not planned and S and I had not been together very long, and were living in separate houses. However, we loved each other and we loved the children we already had so we decided to go ahead as, although it wasn't what we planned, we loved the idea of adding to our family. I do remember thinking about the medication and asking again, the risk was slightly higher for spina bifida as S had an older sister who had that plus hydrocephalus, she died at 2 and a half, nothing else had changed with regard to risk. For me that was reassuring and I thought about the fact that my first two children appeared fine, so the risks were minimal. The pregnancy was up and down, I suffered a lot of sickness so I gave up the college course I had started and stopped going to club. When I was 7 months pregnant I had a mild bump in the car which set off labour pains, which fortunately settled. I was in and out of labour for the last few weeks of my pregnancy and my stomach was getting tighter and tighter. Eventually they decided to induce a few weeks before term because of this. K was born very quickly weighing 8lbs 12oz. He was adorable but my cuddles were short lived as he turned purple and his appgar score dropped. This meant that he was then taken away to SCBU (Special care baby unit) and put on a drip and oxygen. I couldn't go with him as by this time I had started to haemorrhage and was waiting to see if I needed to go to theatre so couldn't be moved or have the canula taken out of my hand. It eventually settled and I was allowed to go up to the ward but I was devastated that my baby was not with me and all I had was a photograph on my bedside cupboard. I was allowed to go up and visit him later in the day in a wheelchair and was able to spend a bit of time with him. It was amazing when I was allowed to try feeding him as I had not been allowed to with D and J. I had thought it would be the same this time round so again whilst pregnant I questioned this and said I would have to bottle feed. This time round though I was surprised and delighted to be told that I could feed, the health visitor told me that there had been research done and I was fine to feed him now. It was discovered that K had a floppy Larynx,

collapsed lung, and clicky hips. After a few days, K was allowed down to join me on the ward downstairs before we came home.

When home it became apparent that he also had sleep apnoea and although his lung re inflated, his larynx remained floppy for many years. He developed bowel problems also. Fortunately at his 6 week check his hips appeared to have settled. The nights were long as K never slept for very long and we had to constantly monitor him when he was asleep, fortunately when he stopped breathing he would gag and wake up but it was still a constant worry. I had a fall when K was just a few weeks old that left me with a broken foot and in plaster for several weeks. This increased the pressure on S as I could no longer help with the night feeds as S would have to still get up. To try and help with K's sleep I attended a baby massage course, but it didn't seem to help and it certainly didn't make him relax like the other babies. J used to come with me and I was shown how to massage her legs as Jade had started to struggle with a lot of leg pains that were so bad they would make her cry and disturb her sleep. Because of all the extra help our children were needing, S resigned from his position at the club and our children stopped going. When K was a baby J had a bad fall downstairs and damaged ligaments in her ankle and both of her wrists. We had to ensure she had help at school and we had to cut up her meals for her.

I discovered, when K was just 8 months old, that I was pregnant again, despite being on contraception, breastfeeding and having needed a D and C after the bleeding didn't stop when it should. This caused me a lot of worries as to how I would cope as K was such a difficult baby it was already having an impact on what we could do with our older kids. Around that time also K had exploratory surgery to try and get to the bottom of his breathing difficulties. I knew we would proceed with this pregnancy too though, as we loved our other children so much. We didn't know that the problems that K was having were most likely linked to my medication until both boys were much older.

The pregnancy went smoothly and C was born at term weighing 10lbs 3ozs. I had tried to be as relaxed as possible during labour, sipping tea and doing crosswords so I refused a pethidine injection or any other pain relief until it was too late and all I could then have was gas and air. C's extremities were a bit purple, and there was a knot in the cord and it was around his neck when he was born. It was lovely to be able to bond with him immediately and I was able to feed him and take him to the ward with me. When C was three months old I went to be sterilised as we felt we couldn't cope if we had any more children as K and C were so difficult. C was so clingy at this point I had to take him to hospital with me whilst I had surgery and I recall coming round and having to feed C whilst still semi conscious.

When we came home we soon noticed that C had the same sleep apnoea as K, sleep became a thing of the past. C never settled though as he would only stop screaming for me until he was about 6 months old. He had a dimple at the base of his spine which someone described as incomplete spina bifida, but it didn't appear to be causing him a problem so we just had to monitor it and make sure it stayed clean. C also developed severe constipation which resulted in hospital stays and a district nurse coming to visit on a regular basis to administer suppositories.

K had his first febrile convulsion when he was about 8 months old, I will never forget the fear I felt as he started turning blue and foaming at the mouth, we had a couple of health professionals with us at the time and they advised that we call an ambulance. That was the first of our blue light experiences, little did we know it would be the first of many. He had a couple more after this one and it was linked to high temperature from the frequent ear infections that K suffered with. When K was two he had surgery to remove his tonsils and adenoids, and have grommets inserted (A developmental check had discovered that he had reduced hearing, so after referral to the ENT at Queen Alexander hospital it was discovered Kyle had glue ear). K had been under speech and language service since he was 18 months old due to a delay in his talking. C was to follow that same route of delayed speech and years of therapy.

C had his first blue light at a year old, when he climbed on the sofa and fell off and knocked himself out. When we were kept in the hospital overnight, C climbed on a chair and fell off whilst I was getting changed.....he left the hospital with more bruises than he arrived with! It was his first blue light but not his first hospital stay, this was a regular occurrence with his constipation.

I had been attempting toddler groups with K, but he seemed to struggle around other children and was becoming increasingly violent. I tried to carry on going after C was born but it was impossible, C would be continually feeding or screaming and K was not able to be left unattended with other children whilst I saw to C so I stopped going. I was becoming increasingly down with everything and was then diagnosed with postnatal depression. It was becoming increasingly difficult to leave the house on my own. S was surviving on 4 hrs sleep a week, everything was putting a tremendous strain on the family as a whole.

The health visitor arranged for me to have a college student come in four days a week for a month to ease some of the pressure. After that Homestart came in and a volunteer began coming out once a week for four hours to enable me to do something. I started back at college so that I could look at building a career as the kids got older. When I started my AAT course K and C started going to a child minder. They struggled with the change in routine and the other children, the food they were being given was not what they would eat at home and it was becoming harder and harder to get them there. C's buggy would remain there but he became possessive over it and would hit anyone that went near. I had no choice but to keep sending them though as I needed to work as part of my AAT so I got a job as an Officer Manager and Accounts Assistant at a local building firm. Unfortunately, despite enjoying my job and feeling a part of something outside of the family I had to resign after 3 months. This was because I was so tired I was struggling to function, and the boys were becoming more and more stressed going to the childminders, it was heart-breaking leaving C sobbing each time, and K was becoming increasingly violent.

In the meantime, I had fallen badly whilst in London with the kids and it had left me with a concussion, sprained thumb, jarring to my back, but it also brought on arthritis in my knees where I hit them. This caused my mobility to become more and more reduced as the arthritis got worse and spread. My balance is poor so I have a tendency to fall a lot, it was getting harder to get back up and now I could no longer do the activity that I used to do my weight

was creeping up. The weight was not helping with the fatigue, so by resigning I could at least carry on with the college course and the boys only needed to go to the child minder once a week.

Before my course had ended the strain had taken its toll on S and he had a breakdown and after year had to make the decision to come out of teaching. This was so hard for him as he had retrained in his late thirties so that he could work in a job that meant he could have the holidays off with S, he was a single dad at the time. It was so difficult to have to give up on the career he had spent years training for because his lack of sleep meant he couldn't cope any more.

D was having his own struggles with school and couldn't cope anymore, so he moved from Felpham to Midhurst Grammar. He had an accident shortly after starting there that left him out of school for 6 months with post-concussion syndrome. This resulted in him needing extra care also. D struggled for the rest of his school years, he had few friends and was confused over his identity so would change clothing styles on a regular basis.

When I completed my AAT I was offered a job working at the college as maternity cover. At the end of the term I was offered the full time position permanently but I had to turn it down as I knew the boys would not cope with such a huge change to their routine and I couldn't commit to a full time. I carried on my plan to set up my own business doing accounting, something I could work around the boys difficulties and helping S to feel better. During all this, J started secondary school.....it was a disaster. She struggled with the journey to school (a window was broken next to her face on her first week and a friend had to take her on a bus journey to regain her confidence- I couldn't do this as I was in plaster again at the time). The school environment was also difficult and eventually she was refusing to go in, this resulted in J being out of school for 6 months before we could get J moved from Chichester Girls High School to Felpham Community College. J struggled to reintegrate with her friends from Primary and eventually made a new set of friends. However, she continued to struggle and eventually she would end up spending large amounts of time in the student support centre.

K started primary school at the same time that J started secondary. We were worried at how he would cope as he had been identified at nursery as a child with special needs. C was later identified in the same way. K seemed to be doing well at school he loved to learn. By the end of year one he was reading library books and would take an encyclopedia to bed with him. It was around this time we really started to see a chasm opening up between him and the other kids. For C this gap was already there, even at nursery. Both K and C struggled all through their primary education, friendships were few and far between and party invites became a thing of the past as they became more and more isolated from their peers. K was referred to the local CDC in year two where they diagnosed him with Aspergers, for us it helped explain his behaviours. Because of this I was made to attend a parenting class and then I joined their Autism support group. I found the support from others in a similar position invaluable so I then set up my own support group which I have been running for 12 years now.

J had started to suffer with severe abdominal pains and ambulance trips and admittances became a regular thing for her. She struggled with these for the whole of her teenage years

and into her twenties and when they couldn't find a physical explanation they sent her for psychological evaluation. The conclusion they decided on was that she was suffering with FEAD ( Food eating avoidance disorder), that must have been caused by the stress of living at home!!! It was so devastating as a mum to be told this and it certainly didn't help J in any way. When she finally moved across to Adult services this was later changed to Crohn's and hypermobility.

When the boys were about 7/8 a friend came over with a newspaper cutting that was to change our lives. It was just a small box that she had cut out of one of the National Papers, but it was about a court case that had begun against the drug company Sanofi. The case was about children who had been born with disabilities due to their mother taking Sodium Valproate in pregnancy that was one of the drugs I was on and had been since I was about 15. Things started to fall into place and make sense. Suddenly it didn't feel like bad luck that our children had so many problems, there was a reason behind it. That was also accompanied by an overwhelming feeling of guilt though, the thought that I was the reason my children struggled so much was like a knife going through me, and even though I had followed all the advice given to me it was a feeling that would never fully leave me. After reading this I got in touch with The Organisation for Anti Convulsant Syndrome and that was the beginning of a whole new journey.....

We were told about symptoms of the syndrome so we contacted the solicitor to register K and C in the court case, fortunately K was just inside the 10 year limitation. We applied for legal aid and once the certificates were through we were sent to see Peter Turnpenny, a geneticist in Exeter. He confirmed that on the balance of probabilities both boys were diagnosed with Fetal Valproate Syndrome. This was done by medical and school records, facial photos from when they were babies/ toddlers, and when blood tests ruled out Fragile X Syndrome. Although it meant that I would carry on feeling the guilt, it also brought feelings of relief. Now we knew what it was maybe we could help our kids more, maybe we would get more help from schools and outside authorities. Also, being included in the court case gave us hope, hope that we could get justice and a secure future for them. (Details of Court case further down).

This turned out to be the complete opposite.....instead of making our lives easier, things were about to get a lot worse. We applied for the boys to get Statements of Special Educational Needs so we could get them into appropriate schools for their needs, and allow them to build friendships in a place where they would be accepted. This was a battle that would take four years in total, and a process that led us to be ostracised within the school community. By fighting for our sons we were seen as the enemy and the school fought us in every way possible. While this was going on the boys were getting more stressed in an environment that wasn't right for them. K became more violent at home and at school, C became more violent at home using all his energy to blend in and hide whilst at school. The effort of all this caused him to start having regular night terrors and increasingly worse asthma attacks. Whilst this was going on things were deteriorating at home and it was getting harder to do things as a family unit. It was suggested that we apply for a Carer's Assessment to see if we could get some external support.....it was the worst thing we could have done! We got a trainee social worker who listened to what we had to say, went to see the school and decided that because

they were the professionals we must be lying. The school wouldn't believe the diagnosis of Fetal Valproate Syndrome so neither did social services. They decided we must have Munchhausen's by Proxy and our children were put on the at risk register. It was a terrifying and humiliating two years. If we went to any appointments that were medical or educational then it came up on the screen.....we were marked. It didn't matter that our boys had a diagnosis from a top geneticist who was a specialist in the field of Fetal Anti Convulsant Syndrome, it didn't matter that both boys had a diagnosis of Autistic Spectrum Conditions, it didn't matter that K had already been granted his Statement of Special Educational Needs, it didn't matter that both boys had been in receipt of Disability living Allowance since they were babies.....none of it mattered. The school said that we told our children what their diagnosis were and they behaved accordingly!! Apparently we told K he was Autistic so he behaved as though he were Autistic!! We had to have a social worker come out every ten days to check we were not harming our children, and we had to attend regular child protection meetings where we were discussed like criminals and made to feel like the scum of the earth. The dr from CAHMS stood there and said she knew nothing about Fetal Valproate Syndrome but in her opinion they did not have it! As she had stated that everyone took note of what she had said and ignored the diagnosis of Peter Turnpenny, the specialist. We were accused of taking our children to hospital, unnecessarily when they were injured, if we hadn't I'm sure we would have been accused of abuse. We finally got a social worker trained in disability, third time lucky. On his visits he acknowledged that our kids had special needs but said as the process had been started we would have to follow it through. It was a thoroughly soul destroying experience that left me swaying between tears and anger, but also tinged with fear, fear that it would take one person to add another lie ( the school managed a lot of them) and our children could be taken away. It was two years that nearly ripped our family apart and the strain it put on our mental health was unreal. Everywhere I went I would hold my head down, I didn't want people talking to me or noticing I was even there. I felt like I was being judged everywhere I went and every time I spoke. Finally they could not argue against the facts anymore and even though the school wanted it to continue, social services called an end to it and K and C were placed on Child in Need plans, this at least gave them access to direct payments and to then have PA's (personal assistants) to help them to go out and to access activities. I don't think I have ever really recovered from that whole experience, and I hate the fact that my children had to see me reduced to tears in front of a roomful of judgemental strangers. Whenever we have to attend meetings at Durban House, be it for educational matters or regarding the direct payments, I am reminded of that time and it feels like yesterday rather than over 10 years ago.

We tried to get back to normal but C continued to deteriorate at school, especially after K left and moved to his first specialist placement, Littlegreen. It was such a relief to see K making friends and enjoying school for the first time in many years, but so hard as it made C's struggles worse. Eventually C could cope no longer and he ended up refusing to go to school completely. We decided that we were not going to risk his health and more damage to his mental state so we kept him home whilst we continued to fight. After nearly a year of being out of school he was placed in a specialist provision for Dyslexia that would also support his Autistic Spectrum Conditions. ADHD and other difficulties, Northease. Like K, C started to develop friendships and enjoying school life. He had been written off as stupid in his primary school, Downview, and when he left he still struggled to read or even write his own name. Finally he was somewhere that understood his needs and taught him appropriately. I will

never forget his first day when he came home crying. We asked him what was wrong and he replied that everyone had wanted to be his friend and he hadn't known what to do.

Both boys started to flourish from this point, and for a while things were fairly stable. We would still have our trips to A and E, K was very accident prone and due to his sensory issues felt the pain more than others might, he was also blood and needle phobic which didn't help. C would often break bones in his fingers and toes and would not even notice for several hours due to having such a high pain threshold. Asthma caused lots of problems for C as he developed a love of sports that he had hated previously, which led to him often collapsing on the field as he didn't know how to pace and would also push himself to the limit, needing constant reminders to use his inhalers. As the boys grew the joint pains they had struggled with got worse too and this in itself could be debilitating ( as a young child we would have to take a pushchair everywhere for C or give him piggy backs as he had such severe pains in his legs he would stop, sit down and then scream).

When K was 14 things changed at school and they started sending him to the local college on day release. K's anxieties became so severe he was suicidal and we had to spend all our time watching him, keeping him safe. He was referred back to the local CAMHS (Child and Family Mental Health Services) where he was seen regularly by a psychologist and then embarked on 8 months of play therapy. It became more of a struggle to get K to school and eventually we had to make the decision to support him in changing schools. He opted to try C's school as he was doing so well there, it was a disaster. This just proved that what is right for one does not necessarily mean it is right for another. Within two weeks of being there the school had to call an ambulance for K, and this was not the only time. This was because he had shut down and collapsed. This started to become a regular occurrence and Epilepsy was thought to be the cause but EEGs and scans ruled that out so they decided it was his mental health and the only way his brain could cope with the overload of anxieties was to shut down, it was a terrifying time. In the end K was unable to attend anymore, he worked from home just going in when he needed to sit an exam. Whilst he was there either S or I had been the ones to take him then wait around for the day then collect him again as he couldn't cope with a taxi. For K it was yet another educational setting that had let him down. K now has to take medication to help him with his moods and anxieties and is seen at the local adult mental health services. K also has weekly sessions with an OT and SALT at college, outside of college he has weekly sessions with a support worker from Autism Sussex.

For C it was the best thing that could have happened to him. C had his ups and downs but he went from a boy with no friends, unable to read or write to become one of the most popular kids at the school with lots of friends. He achieved 9 GCSE's and his Bronze Duke of Edinburgh Award, and at 14 he was given an award for his contribution to disability sports from a disability youth group that he attended and where he later volunteered.

Despite all of this K achieved most of his GCSE's and chose to go on and study his A levels. For this he needed an appropriate environment that would enable him to do so. Eventually, after several months of looking we found a college in Brighton that was 1-1 tuition with a maximum of 15 students in at any one time. The first year was a struggle as the Local Authority were refusing to put in the support that was in his EHCP (formerly statement), this

meant that he deteriorated again and after going through three tutors K eventually dropped Art. This meant he had to choose two new subjects and do an extra year there.

When C completed his GCSE's the Local Authority let him down too, they removed him from his specialist placement over the summer holidays and placed him directly into a mainstream college that was so far away he had 3-4 hrs travel a day, when on some days he only had one lesson, 5 days of the week. This left us with another battle and another appeal, in fact this tribunal took us back to The Royal Courts of Justice in London where we had been going for hearings in the Epilim Litigation. C got back his boarding place at Northease which eased the fatigue around travel but he still wasn't getting the provision within his EHCP and he started distancing himself from his friends.

Educationally, for the last 8 years the boys have had to travel for between 3 to 4 hours a day because the only provision available was that far away. This has meant any friends they made were not local and were often too tired to do things outside of school. For the last five years S has had to drive K which has impacted on S's fatigue too. Both boys are due to finish the current stage and embark on the next part of their educational journey, so our next battles are about to begin I'm sure along with a new set of anxieties.

When joining the court case, I also volunteered to join the board of OACS as treasurer so that I could help support others like us and help a charity that had given us answers and hope. I remained on the board for about 8 years, with S joining about a year after me. Due to logistics only one of us would usually attend the board meetings and court hearings, which was usually me whilst S held things together at home. I remember the anger I felt at my first ever hearing when the Sanofi Barrister stated that epileptic women should not be allowed to have children as they were bound to be defective. I was so angry I drew a picture of said barrister with my fist coming down on his head, and another into his cheek..... a statement I will never forget. The court case itself held its own stresses, especially when C and then K were selected as test cases. This meant we had to travel up and down the country whilst they attended different assessments. One that we went to was for K's autism where we travelled to Newcastle, subsequently K's diagnosis of Aspergers was changed to A-typical Autism following this. The one benefit from this was that when the court case folded we were allowed to use these reports to help them with their educational needs, and it helped identify their difficulties. The downside was that we had to keep leaving our older children at home whilst we went off on the trips and the boys increasing needs made the older children feel more left out, less important. As time went by my mobility got worse and my anxieties increased so S started coming on the trips to London too whilst we left our children at home with a PA. The demands of the court case and of the charity meant that Fetal Valproate Syndrome had completely taken over our lives. We were continually filling out paperwork either for the trial or for OACS. We had the strain of our battles with social services and schools alongside this. The more we discovered the angrier I became at how my children's lives had been changed so much because it was decided we shouldn't know the risks associated with the medication we were taking. We were never given a choice, and having the information would have allowed us to make an informed one.

Then one day the funding committee decided that the case didn't have a high enough chance of success and our legal aid was withdrawn, this was after years of preparation and just weeks before the main trial. The drug company had won even though we never made it to court, the government had enabled them to walk away. Even though I would have had to appear in the witness stand, a thought which terrified me, I still had been denied my opportunity to tell our story, to talk of the struggles my children faced because of the medication I had taken. We were told also to sign a disclaimer saying we would never take Sanofi or any of its associated organisations to court in the future, otherwise they would come to us for costs and we would lose what little we did have for our children's futures. We appealed to the government to change their decision, we went to media in an attempt to get the decision changed, but it was all to no avail and six months later it finished. It added insult to injury when the same day of the final hearing in May 2010, Sanofi released a new PIL stating that Epilim could cause Autism when they had denied this all through the preliminary hearings. OACS trustees decided that they wanted to continue fighting without the constraints of a charity so a new Trust was set up (FACT-Fetal Anticonvulsant Trust). The aim of this was to continue campaigning for justice and compensation for all of the children and families affected as like us so many were dependant on the state as they were a family of people affected by disability or caring. The pressure was taking its toll on S who was already struggling after having broken his neck a few years earlier. Surgery had made things worse and affected his mobility and he had also developed Fibromyalgia from the trauma. The added stress from all this eventually put him in hospital with a suspected heart attack and because he was not able to work as much for the charity whilst he recovered. This resulted in conflict amongst trustees and left S and I running OACS from home whilst things were pieced back together again. After two years we decided we couldn't continue like this anymore and we reluctantly stepped down and passed the reins over to a new board to carry on the work. The Trust had been working with the Thalidomide Trust to guide us and the wheels had been set in motion to set up an APPG to look into the failings surrounding the scandal of Sodium Valproate. Unfortunately, when S became ill things changed and moved in a different direction.

We have continued to support OACS in whichever way we can and will always fight for our children. One day we hope we can get the justice they deserve and a future that will be secure and not full of uncertainty. One thing we know for sure is that the children will not grow out of their health issues in fact they seem to have got worse as they have got older. J's joint pains and bowel problems continued and she ended up having to use a stick by the age of 19. D has developed severe mental health difficulties as he has got older which has impacted hugely on his life. K has now been diagnosed with an anxiety disorder along with his other difficulties and is under investigation for his sleep apnoea again. C seems to be developing an increasing number of problems with different foods and wants to just be the same as everyone else so he continues to be the chameleon, blending and changing to fit in with those around him.

I still carry the guilt of having taken the drug that harmed my children, with knowledge I could have made different choices. More than anything I feel anger and a sense of loss for the lives we could/should have had instead of the daily struggle we have instead.

XXX

## **Other comments received by OACS**

*“To be honest, disgusted, these children and families have been let down not just by Sanofi but by the government, by the system, by the NHS, fighting for basic care, disability benefits, chasing professionals, it's pretty disgraceful, we as a family have been put through hell, called liars told we are fabricating our daughters condition, which is absolutely ridiculous, the ignorance and lack of education surrounding this catastrophic, debilitating rare disease is as bad as the disease itself, knowing this man made condition could have been stopped is heart-breaking”*

*“I worry about the future, I worry about what will happen to my gorgeous little girl, when I'm gone, we feel hopeless.” “As a family, we don't go on holidays together”*

*“My Son keeps asking questions that I cannot answer regarding his future”*

“I have lost our house due to the cost of caring for a child with FACS, we had a mortgage before all of this started but increasing medical expenses, there was no way out” “My career has been impacted due to the time that I needed to take off work, for many hospital appointments and operations”

“As a family, we lose out on family gatherings, with friends and family because my Son's continuous meltdowns”

“Watching your child grow up with no friends at the age of 17 is heart breaking”

“Your child not being able to learn to drive like any other 17 yr olds”

“Watching your child being bullied at every level of school and not having an answer”  
“Knowing that you may never become a grandparent”

“Knowing that your Child will never have total independence, living on their own or with their own family”

“Worst of all the feeling of watching other children giving hugs and cuddles to their Mums, knowing it will never be like that for me”

“Even the simplest thing of having an engaging two-way conversation never happens in our family life”

"It's hard to imagine what normal life would be like, it's been like this for 17 years now. Whenever you think that you have things under control, something else happens to our child's health and wellbeing because of FACS"

"We long for our child to experience life, like other children" "All any parent desires are that their Child grows up into a fine young man or young lady, set up to go out in the big wide world."

"Watching my child laying in a cot bed at the age of 19, whilst my other children go off to hospital appointments with their own chronic health conditions caused by Valproate"  
"Attending to all my child's personal things like washing her down 3 times a day, putting nappies on her, feeding her most of the time by mashing up her food so that she doesn't choke, dressing her and changing bibs to catch her saliva is just part of her daily routine"

"I am mourning my child now and will be mourning the death of her when she's gone, this is the result of Valproate, no parent wants to see their child slowly die in front of them"

The following responses were collated by OACS and FACSAware in response to a questionnaire made available to all members through their websites during March 2018. These responses have been anonymised and reformatted by Leigh Day for the purpose of providing evidence to this Review.

**1. KL (Anonymised)**

**What age were you when you were prescribed Valproate?**

My GP thinks 1999. Hospital might be different. I am in the process of getting records to confirm this.

**What warnings were given to you or your parents?**

Nothing when I first took it. Then I fell pregnant when I was 17, and thought there might be side effects. I asked my doctor and they said there was a very low risk. 4-5%

**How many pregnancies have you had?**

5 in total:

1<sup>st</sup> - born in 2004 – suffers from spina bifida and hydrocephalus

2<sup>nd</sup> daughter born in 2011 – no health complications

3<sup>rd</sup> pregnancy was in 2014. The scans at around 12-16 weeks revealed that this baby also had spina bifida and Edwards syndrome. I was asked if I want to carry on. We decided that we couldn't care for another child with spina bifida so we had to terminate.

This was when I decided to stop taking valproate. I started taking Keppra instead.

4<sup>th</sup> - born in 2016 – no health complications

5<sup>th</sup> – Daughter – born 5 months ago – no health complications

**Surviving children**

<b>Child 1</b>	
<b>Name (Anonymised)</b>	<b>KL</b>
<b>Year of birth</b>	<b>2004</b>
<b>Does child have an Education Health Care Plan or Statement of SEN</b>	<b>Yes. He is in an Specialist Teaching Facility unit at school Struggles to write his name – struggles to hold the pen</b>
<b>Will child have full capacity to live independently as an</b>	<b>No. He is in a wheelchair and will require full time care.</b>

adult?	
<b>Services required:</b>	
<b>HEALTH</b>	
<b>Operations</b>	<p>He couldn't be taken out of hospital until 4 months old because of the range of operations he had to undergo.</p> <ul style="list-style-type: none"> <li>• Operation on his head when he was first born. Had to open his head to put in a VP shunt</li> <li>• One on his spine</li> <li>• Operation on his feet – telephies</li> <li>• One on his belly – has bladder and bowel issues</li> </ul>
<b>Therapies</b>	<p>He has physiotherapy to make sure his posture is right.</p> <p>He has Lymphodema in his feet and requires foot massages for this.</p> <p>Has to be catheterised 5 times a day. Has to have a bowel wash every night as he isn't able to go to the toilet properly. He can't feel when he's going. The bowel wash flushes him out every night</p> <p>He needs to have more We have been talking with the social worker to try to get this to happen.</p> <p>As he is getting older we are seeing more problems. He feels so insecure that he can't even speak. He has to communicate in sign language. If he knows you very well he will talk. But if he has never met you before I have to be beside him to help him.</p> <p>I know when he comes out of school he won't be independent like others. I know he doesn't have the head for it. He struggles with maths. He can't control or understand money. Someone has to be with him 24/7.</p> <p>Caring for him is getting even harder now that he's getting bigger. He likes routine. If we say he can't do something tonight, he won't understand why. He</p>

	<p>doesn't realise how strong he is. Got to massage his feet</p>
<b>Diagnosis</b>	<p>Spina bifida and hydrocephalus Epilepsy. He has seizures where his eyes roll back – petit mal. This is getting worse as he gets older. Horseshoe kidney Lymphodema on his feet</p>
<b>Prescriptions</b>	<p>Medication to maintain urine in his bladder. - Oxybutinin Epilim for his epilepsy. Tablets for urine infection.</p>
<b>Assistance aids (glasses, support boots, hearing aids etc)</b>	<p>He has lymphodema on his feet. His feet get quite swollen from shuffling along the floor. He has to wear special boots for this</p> <p>Wears nappies, catheters. He has an aid on the side of the toilet to help him get on. We have to live in a bungalow. Special hospital bed – needs to be changed quite often.</p>
<b>Hospital inpatient admissions</b>	<p>At Cardiff - every 6 months for his horseshoe kidney. Measure his head. Make sure the size is ok.</p> <p>KL has to go to the doctors quite often because he gets urine infections all the time.</p> <p>KL has accidents a lot – if not wearing his boots he will hit / burn his feet. Because he can't feel. Recently he had a burn on his foot from the radiator, which then got infected. This took a while to heal.</p>
<b>Other</b>	
<b>What will child require in the future as an adult?</b>	<p>More operations. BR spoke about him having a hole in his belly so he can do his catheterisation himself. His father said no for now but this may be necessary as he gets older</p> <p>Stoma for his bowels. Difficult to say what he will be able to do himself. Will need to be lived with until his</p>

	<p>30s.</p> <p>May need to live in a care home.</p>
<b>EDUCATION</b>	
Pre-School	<p>Stepping stones for people with special needs to try to prepare him for primary. Therapy sessions at him in</p> <p>3-4</p>
School	<p>School has been very hard for KL. He has always been in an STF unit.</p>
Further Education	<p>We want him to be at school until 18. Want to get him to learn independence but I think he will always need support.</p>
Other	
What will child require in the future as an adult?	
<b>CARE</b>	
Local Authority (council)	<p>We do not have much support from the local authority.</p> <p>Years ago – when he was 8 or 9 - he would stay over at a disability support group for 1 night every fortnight. This has closed down now. It was called Seizing the Challenge.</p>
Health services	<p>Got carers</p>
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	<p>DLA – have asked for the higher care component. This needs to be increased as he requires 24/7 care.</p>

<b>Benefits awarded</b>	<b>Currently on middle care component. Higher mobility component.</b>
<b>Benefits withdrawn</b>	<b>No</b>
<b>What will child require in the future as an adult?</b>	

### **Career and Lifestyle**

Are you in paid employment? No

What is your occupation? N/A

Are you struggling financially? Not really.

What has been the financial effect of having a child with Valproate syndrome?

It can be hard – have to travel, get the things specifically for them. They don't understand the word no so this can be very demanding financially.

Do you have an active social life? We used to have a few friends but not anymore.

Do you have to make special arrangements if you want to go out? Don't really have much of a chance to go out. KL is so much hard work. People won't come over.

Do you have support from friends and family? No

Do you feel isolated? Definitely. Me and my husband so drained with everything. Don't have the head for anything other than KL.

Have your personal relationships been affected by having a child with Valproate Syndrome?

My father effectively disowned me as he didn't agree with my choice to have KL and look after him. I have lost almost all social contact as a result of KL's disabilities.

Are you a single parent? No. Married.

What effect has having a child with Valproate Syndrome had on your lifestyle?

It is exhausting. My whole day is given over to worrying about KL and making sure he has everything he needs. I know this will continue for the foreseeable future. We cannot go out and do anything for ourselves. Everything has to be about him.

### **2. MN (Anonymised)**

I was diagnosed with Epilepsy in 1990 and commenced Sodium Valproate. I married my husband in September of 1997 and in 1998 sought pre-conception advice from my GP in [REDACTED] about taking Sodium Valproate whilst trying to conceive. I was advised that there was no risk and prescribed a pregnancy multi vitamin (which I took). We moved to [REDACTED] in 2000, by which point I had still not conceived. I again sought pre-conception advice from my new GP, who reiterated the advice to continue to take the Valproate, as the potential risk of seizure was felt to be greater than any risks to the foetus presented by the continued taking of Sodium Valproate. I was not pregnant at this time and as I had not conceived, I was referred to the Fertility Clinic. However, as often happens before the appointment arrived I became pregnant. I visited my GP again, and was advised to start to take folic acid. I recall my GP writing to a Consultant Obstetrician (at [REDACTED]) for advice re ongoing management of my epilepsy during pregnancy. This appointment did not arrive until after my 20 week scan. At the 20 week scan at [REDACTED] the Sonographer found that our unborn child had Spina Bifida and Hydrocephalus.

We were seen the same day by a consultant and our options were given as thus:

- Terminate the pregnancy. We were required to make an almost overnight decision.
- Continue the pregnancy and have planned C-section
- Continue the pregnancy and have vaginal delivery (knowing there was a high risk that the baby would die as result of trauma). I was advised we were given this option in case we had religious objection to termination.

We asked if the findings were a result of the Sodium Valproate and the consultant confirmed that this was likely.

MN was born by planned C-section on the [REDACTED] 2001 at [REDACTED]. She was born with a L3-L4 myelomeningocele (spinal lesion), and hydrocephalus. She was immediately taken for surgery and was in theatre for a nine-hour operation to close her lesion and insert a VP Shunt. MN was resident on the Neo-Natal Intensive Care Unit at [REDACTED] for the first month of her life.

In addition to the Spina Bifida and Hydrocephalus MN was diagnosed with several other associated physiological abnormalities:

1. Bilateral talipes (clubbed feet)
2. Bilateral dislocation of her hips
3. Hyper-extended knees (legs were bent backwards at her knees and were so badly damaged that x-rays had to be taken to determine whether she had knees.
4. Arnold Chiari II brainstem malformation

MN experienced many challenges in her early weeks and months. She found swallowing difficult, an associated problem linked to the Chiari Malformation. She required several shunt

revisions during the first few months, requiring neurosurgery due to shunt malformation, a potentially fatal complication.

We eventually took MN back to our home in [REDACTED]. I could not return to my work as a Ward Sister at [REDACTED] as MN's needs were too great. It became apparent that MN was highly unlikely to be able to walk as had no movement in her legs. At the time our house was not accessible, and we decided we needed to live in a bungalow to best meet her needs. We therefore decided to move to [REDACTED] and we moved to a bungalow in [REDACTED]. We felt a small community and village may be a good place for MN to grow up and we moved there in 2002.

Over the next few years, MN failed to meet the normal milestones for a child of her age.

- MN cannot, weight bear, stand or walk at all. MN uses a wheelchair to mobilise.
- MN is bladder and bowel incontinent, a condition that is linked directly to her Spina Bifida. For years, this was managed by physical interventions completed by us as parents (frequent catheterisation, bowel management through the use of suppositories and, more often than not, the use of nappies, until MN was well into her formative school years. In order to improve her quality of life, we took the decision to engage surgical intervention to support her in managing her basic personal care:
  - Major bowel surgery, to place a caecostomy button to enable daily bowel wash-outs to manage her bowel continence.
  - Major urological surgery; including bladder augmentation, removing a section of her small bowel and patching this into her bladder to increase its capacity. This was in conjunction with the formation of a mitrofanoff, using her appendix to create a conduit from her bladder, through her abdominal wall to enable her to self-catheterise. This enables MN to manage her own bladder continence.
- In reality, MN spends over an hour sat on the toilet every day just to ensure she remains continent. Whilst this is in part successful, MN's continence still presents risk to MN's confidence. On several occasions through her Secondary School career, and even now whilst at college, MN has periods of incontinence that she finds extremely upsetting.
- MN has required several surgical interventions to correct her talipes, to enable her to wear shoes.
- MN wears splints to ensure her foot position is maintained. She wears these every night.
- MN has a low threshold to seizures, and in her primary school years, experienced many seizures, some of which required significant medical intervention. For example, on one occasion, MN's seizure was so severe, she was transferred from [REDACTED] Hospital to the Intensive Care Unit at [REDACTED], as she needed to be anaesthetised in order to control her seizure.

- MN has developed severe Scoliosis and Lordosis (curvature of the spine).
- MN has many associated learning needs associated with Hydrocephalus. She is unable to concentrate for sustained periods of time; she displays several traits of Attention Deficit Disorder, not in terms of her behaviour, but solely with regard to her ability to concentrate and process information and instruction. MN is supported by an EHCP, but has had a Statement of Special Educational Needs since she was 3 Years old.

In general, the impact of Sodium Valproate on MN and our family, has been significant. MN's condition has impacted on our choice of home and our location. I was unable to commit to full-time employment throughout the first 3 years of MN's life, due to complexities of MN's care needs. I had to work unsociable hours to ensure either my husband or I were able to support MN 24 hours a day. It is well-reported that the cost of raising a child with a disability are disproportionately high compared with non-disabled children. We experienced great difficulty securing suitable childcare to enable us both to return to full-time employment in order to make ends meet. MN's first nursery, were initially supportive, but eventually, gave us 12 hours' notice that they could "no longer cope" with her personal care needs as it was "too expensive for them". We resorted to a private child minder, who again, after 6 months terminated the arrangement because MN required too much 1:1 care. Eventually, we discovered [REDACTED] Nursery, who were extremely accommodating and supportive, enabling us to both return to work, by which point we had accumulated significant personal unsecured debt, which still remains a string feature of our personal finance. Although this is well-managed, we anticipate this debt will not be cleared until MN is at least 30 years old.

MN attended mainstream school and was well-supported by [REDACTED] High School. She achieved well in some subjects in her GCSEs, but didn't meet the national standard for Maths and English so is now resitting these at [REDACTED] College. Whilst MN's independence continues to grow, we do not foresee a time when MN's personal care needs will be met independently. She currently works as part-time as a volunteer for [REDACTED] Hospice, in order to build some degree of work-experience, and is thriving in this environment. Despite this, MN remains very socially isolated, due to her continuing difficulty in developing and maintaining social relationships. MN requires careful guidance from us as parents in her communication/interaction with her peers.

MN still requires support to manage her personal care needs. Without regular prompts to self-catheterise, or strong parenting to ensure she completed her daily bowel wash-out, MN would be incontinent. Now aged nearly 17, we do not currently foresee a time when MN will not require this degree of personal support.

Despite her obvious challenges, MN is a wonderful young adult, who has so much to offer society. It is clear to us that the life-long impact of Sodium Valproate on MN's life-chances, social fulfilment and earning potential has been profound. Beyond this, the impact on our family has been equally significant.

We considered the risks of similar issues when planning for our second child, NO, who was born in 2006. Fortunately, I had changed medication to a more suitable anti-epileptic drug, so NO was born without complication. He does however, feel the impact of growing up with a disabled sibling. He is a registered Young Carer; having to accept the quantity of time we as a family are required to dedicate to his older sister. He does understand, and he does support as much as we can expect a child to support. Over time, however, this is clearly having a profound impact on his formative years. NO worries about his sister enormously, but feels the frustration when as a family, we are restricted in the choices we can make as a family; holiday destinations, weekend activities, family days-out, are all subject to our assessment of accessibility. In order to ensure MN is included, NO often misses out on these experiences. An extremely difficult balance to strike as a family.

Back in 2010, we were one of 100 families seeking compensation for our children. Sadly, after a six-year battle, the Legal Services Committee took the decision to withdraw legal aid and the case collapsed. Compensation would be life-changing for MN, as well as the other children affected.

- Financial security, that would otherwise be gained through meaningful employment, rather than a life-time reliant on benefits and Personal Independent Payments
- Guaranteed life-long personal care
- Access to enhanced care and specialist equipment, above and beyond that provided by the NHS, improving health, wellbeing and quality of life.

### **3. OP & PQ (Anonymised)**

**What age were you when you were prescribed Valproate?**

teenage

**What warnings were given to you or your parents?**

none

**Did you ask for advice on pregnancy?**

yes

**How many pregnancies have you had?**

5

Pregnancy	Outcome	How many weeks since conception	Year of death
1	miscarriage	8 weeks	1995
2	miscarriage	7 weeks	1998
3	Miscarriage	7 weeks	1999

### Surviving children

Child 1	
Name (Anonymised)	OP
Year of birth	1997
Does child have an Education Health Care Plan or Statement of SEN	Nope
Will child have full capacity to live independently as an adult?	Nope never
Services required	
<b>HEALTH</b>	
Operations	Teeth out (closely compacted teeth) braces
Therapies	Gp , camhs, fine gross motor skills at school group, scans on his kidneys, wears glasses ,occupational therapy ,haring clinic
Diagnosis	Dyspraxia, autistic, stigmatism both eyes, cysts on his kidneys, low muscle tone, processing issues delayed development, closely packed teeth braces, depression anxiety, bowel problems (incontinence), child clinic, foetal valproate syndrome
Prescriptions	Floxatine anti-depressant, amptrptoline
Assistance aids (glasses, support boots, hearing aids etc)	Glasses
Hospital inpatient admissions	2

Hospital Consultants	5-6
Other	
What will child require in the future as an adult?	Support throughout his life to he can live independent life
<b>EDUCATION</b>	
Pre-School	
School	
Further Education	
Other	Left education ,
What will child require in the future as an adult?	Support with all living and finances in supported accommodation
<b>CARE</b>	Supervision with personal care , and living independently
Local Authority (council)	██████████
Health services	NHS
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	
Benefits awarded	Pip,
Benefits withdrawn	
What will child require in the future as an adult?	Full living support

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Child 2	
Name (anonymised)	PQ
Year of Birth	2001
NHS number	
National Insurance number	
Does child have an Education Health Care Plan or Statement of SEN	Slp
Will child have full capacity to live independently as an adult?	Nope he will need full support with all his daily living and looking after a home
Services required	
<b>HEALTH</b>	
Operations	
Therapies	Cahms, perth autism support, key worker at school case load pupil, child development clinic genetics clinic
Diagnosis	Foetal valproate syndrome ,delayed development ,stigmatism ,behaviour problems ,dyspraxia, processing problems, sleep problems, anxiety , depression, autism, sore bones mobility issues
Prescriptions	Circadian melatonin, paracetamol
Assistance aids (glasses, support boots, hearing aids etc)	Glasses, support aides for writing reading for working tv comp work
Hospital inpatient admissions	0
Hospital Consultants	1
Other	1
What will child require in the	Full support to live independently

future as an adult?	
<b>EDUCATION</b>	
Pre-School	
School	Support at school small classes , caseload teacher, go to place if stressed,
Further Education	
Other	
What will child require in the future as an adult?	lep in college guidance support help with exams single accommodation, extra time , support for looking after himself in supported accommodation
<b>CARE</b>	
Local Authority (council)	██████████
Health services	NHS
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	
Benefits awarded	Pip
Benefits withdrawn	
What will child require in the future as an adult?	Full supported in supported accommodation

### Career and Lifestyle

Are you in paid employment?

yes

What is your occupation?

cleaner

Are you struggling financially?

yes

What has been the financial effect of having a child with Valproate syndrome?

I am unable to get a good job and work full time to give my family the things they deserve ,

Do you have an active social life?

no

Do you have to make special arrangements if you want to go out?

yes

Do you have support from friends and family?

no

Do you feel isolated?

yes

Have your personal relationships been affected by having a child with Valproate Syndrome?

yes

What effect has having a child with Valproate Syndrome had on your lifestyle?

It puts a lot of stress and strain on the family and our marriage , we cant do what we wont to or go where we wont to as it have a massive impact on our life we have no one to look after them for us as their grandparents are over 70 years of age , and is unable to handle any meltdowns as they are over 6 ft tall and well built

#### **4. QR & RS & ST (anonymised)**

**What age were you when you were prescribed Valproate?** I was 17 years old in 1993.

**What warnings were given to you or your parents?** I was told that the long term using can cause liver problems.

**Did you ask for advice on pregnancy?** Yes, before it I had a full medical check-up, I was told there is a 1% chance spinal bifida.

How many pregnancies have you had?4

**Surviving children**

Child 1	
Name (anonymised)	QR
Year of birth	2005
Does child have an Education Health Care Plan or Statement of SEN	In progress right now.
Will child have full capacity to live independently as an adult?	I can't decide it yet.
Services required	
<b>HEALTH</b>	
Operations	
Therapies	He got several types of therapies from age 3 moth-as he couldn't even hold his head, because of hypotonia. Speech therapies and psychologist was working with him as well.
Diagnosis	hypotonia, speech disability, dysphasia; autistic behaviour
Prescriptions	
Assistance aids (glasses, support boots, hearing aids etc)	
Hospital inpatient admissions	

Hospital Consultants	
Other	He has speech disability and hypotonia in his nerve-system. He had problem, but hopefully healed: with his eyes, heart murmur and he was premature (35weeks 1500gr 42cm).Now he is struggling with his teeth as the baby ones are blocking the permanent ones, he will need surgery
What will child require in the future as an adult?	It is difficult to prognose as he has autistic behaviour, doesn't understand the speech well because of the sensomotoric dysphasia, so hard to tell.
<b>EDUCATION</b>	
Pre-School	
School	
Further Education	█ Academy
Other	
What will child require in the future as an adult?	I am hoping he can pass the GCSE test if he will have the chance more, more time to pass it, as everybody can see it now, this is the only chance for him, right now I can't look further, as everything is depending on it. Then later financial support as well to get a special education to learn a profession (something what is not need speech, communicational skills etc.)
<b>CARE</b>	
Local Authority (council)	█ Council
Health services	█ Health Centre
<b>WELFARE BENEFITS</b>	
Benefits you have applied	Housing benefit, Council tax support, Child benefit, Child

for	tax credit
Benefits awarded	Child benefit, Child tax credit
Benefits withdrawn	Housing benefit, Council tax support
What will child require in the future as an adult?	

Child 2	
Name (anonymised)	RS
Year of birth	2007
Does child have an Education Health Care Plan or Statement of SEN	No
Will child have full capacity to live independently as an adult?	Yes, I am hoping.
Services required	
<b>HEALTH</b>	
Operations	
Therapies	Speech therapy, and Ayres therapy
Diagnosis	Speech disability: late in speech development
Prescriptions	
Assistance aids (glasses, support boots, hearing aids etc)	
Hospital inpatient admissions	Several ear infections
Hospital Consultants	

Other	he can't always control the urinating, and he is very small, his growing progress went down
What will child require in the future as an adult?	Hopefully nothing special.
<b>EDUCATION</b>	
Pre-School	
School	█ Primary School
Further Education	
Other	
What will child require in the future as an adult?	Hopefully nothing special.
<b>CARE</b>	
Local Authority (council)	█ Council
Health services	█ Health Center
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	Housing benefit, Council tax support, Child benefit, Child tax credit
Benefits awarded	Child benefit, Child tax credit
Benefits withdrawn	Housing benefit, Council tax support
What will child require in the future as an adult?	I am hoping he will be coping alone

Child 3	
Name (anonymised)	ST
Year of birth	2009
Does child have an Education Health Care Plan or Statement of SEN	No
Will child have full capacity to live independently as an adult?	Yes, I hope so.
Services required	
<b>HEALTH</b>	
Operations	
Therapies	She was born with club foot, had cyst in her brain, special therapies (Ayres therapy) and speech therapy as well
Diagnosis	speech disability, dyspraxia, hypotonia in the nerve system
Prescriptions	
Assistance aids (glasses, support boots, hearing aids etc)	special glasses, special insole
Hospital inpatient admissions	
Hospital Consultants	
Other	
What will child require in the future as an adult?	I am hoping she won't need extra help as an adult.
<b>EDUCATION</b>	

Pre-School	
School	█████ Primary School
Further Education	
Other	
What will child require in the future as an adult?	
<b>CARE</b>	
Local Authority (council)	█████ Council
Health services	█████ Health Centre
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	Housing benefit, Council tax support, Child benefit, Child tax credit
Benefits awarded	Child benefit, Child tax credit
Benefits withdrawn	Housing benefit, Council tax support
What will child require in the future as an adult?	I am hoping she will be coping alone

### Career and Lifestyle

Are you in paid employment? No

What is your occupation? When I am and the kids ok, I am working as a face painter and a crafter so trying to get some money for the living as self-employed.

Are you struggling financially? Yes

What has been the financial effect of having a child with Valproate syndrome? We came from Hungary 3 1/2 years ago. In Hungary we had to pay for most of the therapies and education for the kids, about 60% of our income went for it, and I couldn't go back to work because of their timetables. Our eldest son finished his second year in the school we had to realise there is no chance them to get a suitable profession for them via the education system there. So we sold everything we had and came to live to the UK hoping they will have a future here. The moving costed us so much, now we have nothing, we just live from day to another.

Do you have an active social life? I am trying not to be at home and catch up with people, but it is difficult as we have not too much friends yet, but I am trying to meet people, when I can go for work to a market, festival etc. Additionally, we have no family here and there is no one to ask (the hiring is too expensive for us) for babysitting to go out just even for a night.

Do you have to make special arrangements if you want to go out? We don't go out just with our kids.

Do you have support from friends and family? I have one friend who has health problems, so we just trying to help each other when each other in need.

Do you feel isolated? Yes

Have your personal relationships been affected by having a child with Valproate Syndrome?  
Yes

Are you a single parent? No

What effect has having a child with Valproate Syndrome had on your lifestyle? Totally different life: different country, I have/had to learn a new language-which is very hard for me, no fixed income, no employment status, no owned home, no enough money-my husband has to work day and night to get enough money for the whole family alone, but sometimes it is very hard to pay even the school uniforms or camps etc.

## **5. TU (anonymized)**

My daughter is called TU (15) she was diagnosed in June 2017 with FVS. From the day she was born we knew straight way something was different about her.

A few hours after she was born she was taken to the IC Unit neonatal. She was placed on a

ventilator due to breathing difficulties. While in there they found a hole in her heart and she had to have a blood transfusion for extra white blood cells. She had a large forehead and eye sockets.

As she got older she was very late with her milestones. Her speech was and still is very poor. She has a low IQ, hypermobility in her arms and elbows, sound sensory issues, incontinence, poor memory, autism, mental health issues and hand and feet malformations.

Valproate has affected our family massively. TU doesn't interact with her peers very well unless they have learning difficulties to. Due to her anger we have damage to doors because she has anger outbursts and kicks them. She gets angry and upset because she can't do the same things other teenagers her age can do. This makes me upset and frustrated too because I hate seeing her upset.

She will never be able to live on her own. Her incontinence makes her embarrassed to go out and she has to wear pads regularly. We are waiting to move as our housing situation no longer accommodates our needs. We live in a 2 bedroom flat. My son is 2 I have share a room with him as he cannot share a room with her due to her anger outbursts.

She has to have a reader, scribe and a writer in her exams. She has a TA in school. She supports with her reading, English and Maths. She is still under speech therapy but they are trying to stop this. She is looking at 0's and 1's for her predicted grades in her exams which in the new system means an ungraded mark. Due to her sound sensory its been hard for her in Maths as the students are loud, she regularly covers her ears and sits in the far corner of the room.

At social occasions we have to leave early as the sound is too much for her. When going out she barely travels alone unless its to our local shop or school. She uses a bus pass but not a disabled persons bus pass so we have to pay. The bus drivers do not understand her speech when she says where she needs to go. This also upsets her.

She does receive DLA at the moment but due to turning 16 in March she has apply for PIP.

Due to stress I have had to add Keppra to my other epilepsy medication to keep seizures under control. Its hard as a mother to watch my daughter try so hard yet not get anywhere because of her problems. When she smiles it makes me as I know it will mean she has had a good day. She wants to do so much yet cannot as she is restricted unlike her peers. Due to lack of self-awareness I hate that she is vulnerable. She will never have a normal life and its due to valproate.

It saddens me deeply. We have been refused an EHCP which we are appealing against. I

worried she will find it hard to get a job as job interviews and most jobs require a lot of communication and speech is a very big issue for her she sounds very child like.

I am worried she will not be able to support herself in the future. The autism assessment we had was done poorly the lady rushed us out the door because she had another appointment we had to make a 2<sup>nd</sup> appointment just to finish the questions.

She has been let down massively by the system. She has been missed because she is a well behaved girl and always plodded along. She hasn't always hit her targets but she has gone un noticed. She will need life long support. Sanofi have a lot to answer for the ruined lives of children including my daughter. These poor children have an unknown future ahead of them.

## **6. UV (anonymised)**

My eldest son UV suffers with a speech impediment he was also a very nervous child he also suffered with hearing problems.

When I had my second child VV she was far worse still no warning signs about my meds of my GP. When she was born my parents thought she looked different but never said anything to me but me of course I thought she looked beautiful why wouldn't I after all I am her mother. VV had the facial features of FACS which at the time I didn't know. As she grew older she wasn't like any other child at 5 month's she couldn't roll over she never seemed to respond to anyone she was floppy docs kept telling me not to worry she was fine.

Then at 9 month's old she was admitted to the hospital for broncolitis and the doctor asked if I had any other concerns so I told him he then referred her to child development unit which she attended twice a week.

I had to do physiotherapy on her everyday she also had special equipment at home, support boots, she also had language and speech therapy. They said her diagnose was delayed development but I wasn't too sure. She had one to one at school because she had learning difficulties she also as spina bifida she has had 3 eye operations, deformed bones plus many more problems.

She will never live independently or have children she will never buy a house she barely as a social life finds it hard communicating. VV was one of the children that was out of time in 2010 when David Body was representing the case. My youngest son WV I thought he was ok then at 18 months old he started with status fits he ended up in intensive care unit and was very ill we nearly lost him 3 times he was always in and out of hospital as a child. He was a very quiet

child wouldn't mix with other children all he wanted was his father he seemed to want to be on his own he liked his own company.

WV had speech problems and had to see a speech therapist I had to keep my eye on him at all times because if he had a seizure he could die. I did find it very hard but they was my kids and they relied on me keeping them safe. As he got older he became very distant from everyone he stopped speaking to us and his friends, locked him self in is room he as no confidence he shows no emotion. He also as 2 nieces one is 7 and he won't acknowledge her at all I don't think that's normal he won't get no help or see is GP, I think he as selective mutism.

But it breaks my heart knowing he is shutting me out and I can't have a relationship with him. WV also has like a hump on his back he won't go to see GP he also suffers with an underlying jaw. So that is bits of my life but it has been a struggle with them all but I do it because I love them. My medication was Epilim 2000mg a day

#### **7A. KF (Anonymised) – Mother's Statement**

**What age were you when you were prescribed Valproate?** 15 YEARS - 1987

**How often do you have a medication review?** ANNUAL

**What warnings were given to you or your parents?**

NONE WHEN PRESCRIBED OR AT ANNUAL REVIEWS – THEN WHEN ASKED ABOUT PREGNANCY REASSURED 2-3 TIMES MORE LIKELY TO HAVE PHYSICAL DEFECT, BACKGROUND RISK IS 2 -3 % THEREFORE APPROXIMATE RISK OF PHYSICAL BIRTH DEFECT = 7%. LESS THAN 1% RISK OF SPINA BIFIDA.

**Did you ask for advice on pregnancy?** YES

**How many pregnancies have you had?** 2

**Did your baby die during pregnancy?**

Pregnancy	Outcome	How many weeks since conception	Year of death
1	TERMINATION	12 WEEKS	1994

**Surviving children**

Child 1
---------

Name (Anonymised)	KF
Year of birth	1998
Does child have an Education Health Care Plan or Statement of SEN	YES
Will child have full capacity to live independently as an adult?	NO
Services required	
<b>HEALTH</b>	
Operations	NONE – BORN FLAT, UNRESPONSIVE, RESUSCITATED. INCUBATOR FOR 10 DAYS.
Therapies	PHYSIOTHERAPY SPEECH AND LANGUAGE AUTISM SUPPORT OCCUPATIONAL THERAPY
Diagnosis	GRADE 1 HYPOXIC ISCHAEMIC ENCEPHALOPATHY INCURLING OF TOES MINIMAL JOINT LAXITY AND HYPOTONIA DYSMORPHIC FACIAL FEATURES DIVERGENT SQUINT. MYOPIA GLOBAL DEVELOPMENTAL DELAY AUTISTIC SPECTRUM DISORDER FETAL VALPROATE SYNDROME HEARING IMPAIRMENT HAYFEVER – ALL YEAR ROUND PICA
Prescriptions	LORATADINE – 10MG – DAILY FOR 2 YEARS THEN TRANSFERRED CETIRIZINE – 10MG – DAILY SINE LORATADINE DISCONTINUED
Assistance aids (glasses, support boots, hearing aids etc)	GLASSES SINCE AGE 3 PEDRO SUPPORT BOOTS AGE 2-4 YEARS SUPPORT CHAIR AGE 2-4 YEARS MOULDED CUTLARY

	MOULDED STATIONARY
Hospital inpatient admissions	BIRTH – 3 WEEKS IN NICU.
Hospital Consultants	NEO NATOLOGIST PAEDIATRICIAN GENETICIST ENT CONSULTANT
Other	PHYSIOTHERAPIST SPEECH AND LANGUAGE AUTISM SPECIALIST AUDIOLOGIST SEN DENTAL SERVICES GP LEARNING DISABILITY NURSING TEAM CAMHS PSYCHIATRIST OCCUPATIONAL THERAPIST OPHTHALMOLOGY
What will child require in the future as an adult?	ENT AND AUDIOLOGY BI ANNUAL APPOINTMENTS LEARNING DISABILITY NURSING TEAM PSYCHIATRIST GP ANNUAL OPHTHALMOLOGY
<b>EDUCATION</b>	
Pre-School	PRESCHOOL TEACHER EDUCATIONAL PSYCHOLOGIST LEARNING AUTISM SUPPORT TEAM 1-1 SUPPORT AND KEY WORKER
School	SENCO EDUCATIONAL PSYCHOLOGIST LEARNING AUTISM SUPPORT TEAM 1-1 SUPPORT AND KEY WORKER MAINSTREAM PRIMARY SEND SECONDARY SEND SCHOOL TRANSPORT
Further Education	SENCO SEN SUPPORT

	SEND TRANSPORT
Other	
What will child require in the future as an adult?	PROMPTS TO TAKE PART IN LEARNING OPPORTUNITIES SEN SUPPPORT SENCO
<b>CARE</b>	
Local Authority (council)	FULL TIME RESIDENTIAL CARE AS AN ADULT SOCIAL WORKER
Health services	SPECIALIST SUPPORT IF HE ATTENDS HOSPITAL
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	INCOME SUPPORT CARERS ALLOWANCE DISABILITY LIVING ALLOWANCE PERSONAL INDEPENDENCE PAYMENT WORKING FAMILY TAX CREDITS LONE PARENT OF DISABLED CHILD TAX CREDIT HOUSING BENEFIT COUNCIL TAX BENEFIT DISABLED BUS PASS
Benefits awarded	ALL OF THE ABOVE
Benefits withdrawn	NONE YET – TAX CREDIT WILL STOP WHEN HE LEAVES SCHOOL
What will child require in the future as an adult?	PERSONAL INDEPENDENCE PAYMENT ESA HOUSING BENEFIT COUNCIL TAX BENEFIT UNIVERSAL CREDIT DISABLED BUS PASS

COST.

EXCLUDES HEALTH SERVICES FROM AGE 12. E.G CAMHS, LEARNING DISABILITY NURSING TEAM, ENT AND AUDIOLOGIST, ADULT OCCUPATIONAL THERAPY.

EXCLUDES WELFARE BENEFITS TO ME, HIS MOTHER.  
EXCLUDES LOSS IN REVENUE IN TAX FROM MY WAGES IF I COULD WORK.  
EXCLUDES TAX REVENUE FROM ME PURCHASING MORE IF I COULD WORK.

**Freedom of Information requests – CALCULATED IN 2010**

Health: Hospital and Community:	£6,963
Education: SEN provision:	£317,000
Welfare: Adult Social Care:	£5,257,000
Approximate lifetime cost:	£5,580,963

**Career and Lifestyle**

Are you in paid employment? NO

What is your occupation? PARENT CARER, VOLUNTEER

Are you struggling financially? NO

What has been the financial effect of having a child with Valproate syndrome?

UNABLE TO PURSUE A CAREER SO RELIANT ON MINIMUM WELFARE ENTITLEMENTS.  
FEW MATERIAL BELONGINGS, I PURCHASE NEEDS NOT WANTS, ESSENTIALS NOT LUXURY. NOT ACHIEVED WHAT I PLANNED AS AN ASPIRATIONAL PERSON.

Do you have an active social life? NOT REALLY

Do you have to make special arrangements if you want to go out? YES

Do you have support from friends and family? NOT REALLY

Do you feel isolated? YES

Have your personal relationships been affected by having a child with Valproate Syndrome? YES

Are you a single parent? YES

What effect has having a child with Valproate Syndrome had on your lifestyle?

I CAN'T PURSUE HOBBIES, CAN'T GO ON HOLIDAY TO DO THE THINGS I'D LIKE TO, UNABLE TO PURSUE A CAREER, UNABLE TO MAINTAIN FRIENDSHIPS AS NO CHILDCARE, I DON'T SEE THE SITUATION CHANGING. I GO TO A POTTERY CLASS AND DANCE CLASS WITH MY SON BUT I AM THERE AS HIS CARER AND CAN'T SOCIALISE WITH OTHERS, CAN'T FOCUS ON WHAT I WANT, EVERYTHING I DO IS FOR MY SON. I HATE BEING RELIANT ON STATE BENEFITS.

**7b. KF (Anonymised) - Father's Statement**

**Surviving children**

Child 1	
Name (anonymised)	KF
Year of birth	1998
Does child have an Education Health Care Plan or Statement of SEN	EHCP / Statement of SEN
Will child have full capacity to live independently as an adult?	No

**Career and Lifestyle**

Are you in paid employment?

Not at present

What is your occupation?

IT Support Technician / Engineer

Are you struggling financially?

Not at present, but I have done

What has been the financial effect of having a child with Valproate syndrome?

30% - 40% of my net salary

Do you have an active social life?

Not much.

Do you have to make special arrangements if you want to go out?

Yes - Sometimes

Do you have support from friends and family?

No - except a little moral support (from close friends).

Do you feel isolated?

Yes- Sometimes

Have your personal relationships been affected by having a child with Valproate Syndrome?

Yes, Absolutely. I have largely remained single and the relationships I have had have been short. I see my friends infrequently.

Are you a single parent?

Yes

What effect has having a child with Valproate Syndrome had on your lifestyle?

Not being able to go out with friends or socialise, because I have my son every other weekend and Wednesday Evenings. When I have my son, making sure it's ok for me to take him and it will be an Ok place for him to go (into that social situation).

The fight for acceptance of my child's disabilities and behaviour from Family (every Christmas to date) and friends /acquaintances (All the time).

Because I have to take time out at work (usually holidays) to care for my son and also I have to request frequent flexibility from my employer due to care commitments, parents meetings, statement and IEP reviews.

Thinking of positive activities that my son and I will both enjoy and my sons reluctance to sometimes not want to do an activity – sometimes I feel house bound.

Because being a carer is tiring and draining, not having any energy left for things I would like to do or my hobbies and interests.

Bouts of depression and anxiety / worry.

Becoming a constant activist to help fight for services (NHS, Welfare and Benefits, Transport to school) that are under constant threat of cuts or being totally withdrawn (in this age of Austerity).

Helping my son's mother in campaigning and lobbying for Awareness and change so that Parents (and Potential parents taking Valproate) can make informed decisions. Also to help stop more children being affected by FACS.

Constant worry about my son's future welfare and care, especially after We (me and his mum) are no longer here to support him.

### 8. KC (anonymised)

**What age were you when you were prescribed Valproate?** 11 years old

**How often do you have a medication review?** Currently my reviews are every 6 months.

**What warnings were given to you or your parents?** None.

**How many pregnancies have you had?** Two pregnancies, one on Valproate.

#### Surviving children

Child 1	
Name (anonymised)	KC
Year of birth	1998
Does child have an Education Health Care Plan or Statement of SEN	YES.
Will child have full capacity to live independently as an adult?	No.
Services required	
<b>HEALTH</b>	
Operations	Talipes correction x 3. Insertion of Grommets x 3. Tibial Osteotomy. Primary Laminoplasty Cervical Spine. Tonsillectomy, Adenoidectomy. Bimaxillary osteotomy for a significant class 3 malocclusion.
Therapies	Physiotherapy. Occupational Therapy. Hydrotherapy.

Diagnosis	Foetal Valproate syndrome. Axenfeld- Reiger Syndrome. Autistic spectrum disorder. Learning disability. Thoracic Scoliosis. Depression. Arrhythmia. Tic disorder. Enuresis. Constipation. Pica.
Prescriptions	Bisoprolol. Mirtazapine. Meletonin. Sertraline. Oxybutynin. Laxido power.
Assistance aids (glasses, support boots, hearing aids etc)	Glasses. Hearing Aids. Orthotic Shoes. Hospital mattress. Bed rail. Bath seat. Grab rails.
Hospital inpatient admissions	Many over 19 years.
Other	Community learning disability nurse. Learning disability care manager. Occupational therapy. Physiotherapy. Social services.
What will child require in the future as an adult?	KC will require medical support for the rest of his life. Being 19 he has now been referred from Children's Services to Adult Services and will require long term support from them. KC has mental health issues and has ongoing help for that.
<b>EDUCATION</b>	
Pre-School	████████████████████
School	KC attended ██████ Primary school. ██████ Junior school,
Further Education	KC is currently attending ██████ college.
Other	
What will child require in the future as an adult?	KC will continue to need an EHCP throughout college.
<b>CARE</b>	
Local Authority (council)	████████ County Council

Health services	Social Services.
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	PIP.
Benefits awarded	KC receives PIP.
Benefits withdrawn	
What will child require in the future as an adult?	As KC has a life long illness we will continue to need help financially . We struggle at the moment.

### **Career and Lifestyle**

Are you in paid employment? No

What is your occupation? Housewife

Are you struggling financially? Yes

What has been the financial effect of having a child with Valproate syndrome?

For 19 years KC has been going in and out of various different hospitals around the country, transport is expensive. I have to finance KC's college transport, as he goes to somewhere with a special needs unit which is further from home. KC also needs extra bedding due to his enuresis. We have to buy extra clothing as lots have to be thrown away. We also spend money on sensory items for KC. The list is endless.

Do you have an active social life? No

Do you have to make special arrangements if you want to go out?

KC cannot be left alone. I have to have somebody here with him.

Do you have support from friends and family? Just my parents.

Do you feel isolated? Yes, as people don't understand KC and they certainly don't understand Valproate Syndrome.

Have your personal relationships been affected by having a child with Valproate Syndrome?

Yes

Are you a single parent? No

What effect has having a child with Valproate Syndrome had on your lifestyle?

Over the years each medical issue KC has had have impacted us and our family in different ways. Every time you have to leave your child laying in a hospital bed the difficulty. How hurtful it is when grown adults laugh at your son. The effects are endless; my life is a constant battle and always has been.

### **9. JK (Anonymised) – Mother’s Statement (see also Case Study 4 above)**

My daughter is 15 and suffers from Foetal Valproate Syndrome and this is my statement.

I had never suffered from epilepsy nor did I have any family history of epilepsy until I had my first seizure at twelve then second seizure at fourteen in August 1994. I was finally diagnosed with generalized epilepsy in October 1994 after recurring seizures.

The doctors placed me on carbamazepine however this drug did not stop my seizures.

At 16 I accidentally got pregnant due to an interaction with my medication Carbamazepine and contraceptive pill. I had seizures all through my first pregnancy and had a son on September 6 1996; he was a normal delivery and to this day has had no side effects to Carbamazepine or my seizures. Regular 6 monthly neurology appointments and reviews at the doctors when needed.

In 1996 after the birth of my first child my neurologist wanted me to move to a drug that would better control my seizures and began to wean me onto sodium valproate/Epilim upping the doses until my seizures were controlled.

In 2001 my husband at the time wanted me to have a child with him, however I was unsure due to my medication sodium valproate and I had heard of medication causing defects.

To be sure before trying for a child I made appointments with 2 Local GP’s at my surgery, I asked if it was safe to get pregnant on the sodium valproate medication and made it clear of my concerns. Both doctors had said it was safe and to go ahead and get pregnant however I made it clear that I wanted to see my neurologist first.

I went to my neurologist appointment in 2002, I told her of my concerns of the medication, I asked if it was safe to get pregnant on sodium valproate, she replied that there was a risk of spina bifida and Down syndrome only.

My neurologist also said that she could move me to another drug lamotrigine however she stated there was no information on lamotrigine because of it being fairly new and said they knew the information on sodium valproate and said to me the better the devil you do than the devil you don't these were her exact words. And suggested going with what we know.

She also stated that my child progress could be monitored through ultrasound scans so if there was any sign of Down syndrome or spina bifida I could terminate the pregnancy.

In June 2002 after taking sodium valproate for six years I found out I was pregnant my doctor thought because of my epilepsy they would increase my medication from 5500 a day to 6000 a day.

At my first scan I found out I was carrying twins which I was overjoyed at the idea of twins, at my second scan in August I found out that one of those twins had died. At 13 weeks gestation.

My pregnancy was closely monitored with several scans due to the risk of spina bifida and Down syndrome but was assured by midwives and doctors that all was ok. At 32 weeks an intrauterine growth restriction (IUGR) was picked up in scans the baby was not growing and the doctors decided to induce her at 37 weeks because of the IUGR and concerns over well-being.

Through JK's delivery the midwife was unable to induce my labour for two days and tried several painful treatments and in the end used Syntocinon to induce.

JK's delivery was normal the doctor commented on the leftovers of the miscarried twin still present. JK was in poor condition white and floppy, the nurse took her straight away to the special care baby unit. The nurse brought back a doctor.

The doctor in front of my bed explaining that my daughter had a hole in her heart (Microcephaly) cleft palate and an extra digit, I was devastated especially as I went to such lengths to be assured everything was ok.

Two days later the paediatric consultant explained that she thought JK had valproate embryopathy because of the dysmorphic appearance, which was later confirmed by a geneticist April 22 2003.

JK had to be given 25mg a day of sodium valproate and weaned off the drug as she started Jerking and fitting because of the withdrawal.

JK is now fifteen years old.

Since birth: chronic chest infections, pneumonia, once a month in hospital, with her as the hole in the heart this compromised her immune system, I was given open access to the ward as JK became a regular visitor.

Nasogastric feeding from birth to 1/ 1/2 years of age at 2 hourly feeds with high calorie milk.

### **Operations**

<b>Cleft palate repair</b>	Age 1 ½	2 weeks in intensive care unable to breath on her own
<b>Scoliosis surgery</b>	pending	Awaiting confirmation
<b>Plastic and reconstructive surgery</b>	Right hand, extra digit removal and extra joint from thumb removed	Physiotherapy at home and at hospital
<b>Plastic and reconstructive</b>	Removal of had brace holding wrist in place	
<b>Plastic and reconstructive surgery</b>	Left hand, extra joint removal from thumb, webbing increased	Physio and occupational therapist for home and school
<b>Pins in hips</b>	Pins placed in right hip due to dislocated hip	JK was unable to walk till she was 9 so her hip dislocated
<b>Pins taken out of hip and loosening on ligaments</b>	Pins removed from hip operation on back on left leg to loosen tight ligaments	Due to not walking ligament got tight  Physio care and splints
<b>Teeth removal and tongue tied operation</b>	Teeth removal and tongue cut from the bottom of mouth	
<b>Investigative surgery Ears</b>	1 <sup>st</sup> operation Found retraced ear drums, Cholestatoma	
<b>2<sup>nd</sup> ear operation</b>	Removal of cholestatoma Age 14	4 hour surgery
<b>3<sup>rd</sup> surgery ear</b>	Removal of packaging in ear	1 hour surgery

<i>Therapy</i>	<i>School</i>	<i>Home</i>
<b>Occupational therapist</b>	From birth to present Seating support chairs equipment	From birth to 12 Seating support, feeding tables, bath and shower support
<b>Physiotherapist</b>	From birth to 9 full weeks in school with physio to improve muscle tone, help her walk. From 9 till present PE hydrotherapy for hypermobility Recovery after surgeries	From birth to present building muscle to the legs to help walk using walking frames physio taught to me by the physio to help her recover from surgery's And ease her pain from hypermobility in winter
<b>ENT</b>	Continuous ear problems	
<b>Podiatrist</b>	Bunions feet problems	
<b>Continance nurse</b>	Bowel blockages from birth to present needs constant management	

***Diagnoses to present date***

- Foetal Valproate Syndrome
- Atrial Septal Defect
- Microcephaly
- Severe Scoliosis thoracic
- Hypermobility
- Recurrent Ear infections and narrow ear canals
- Anxiety and Hyperacusis
- Self-harming Behaviour
- Severe learning disability age 3/4
- Full time continence pad or nappies
- Sensory Processing Disorder
- Bone growth delayed

**Health and mental health**

JK suffers from severe developmental delay at age ¾ her understanding of feelings and anxieties are hard for her to comprehend.

JK suffers from hyperacusis and anxiety caused by improper treatment of hyperacusis over the year by many untrained professionals.

JKs hyperacusis was only noticed at about 6 or 7 when she started talking and was more mobile by use of walkers and specialist wheelchairs

She tantrums because of her noise sensitivity this has become worse as she has become older. In the summer and Christmas JK won't leave the house because of how busy it gets and the noises in public places like children screaming, babies crying, toddlers having tantrums and dogs barks any high pitch noises.

JK anxiety is caused by her noise sensitivity she likes a controlled environment and has problems going to new places because she has a fear of the unknown noise that might be there, this makes it difficult to place her at a school right for her.

JK had hypermobility this become painful in her joints in the winter months where I have to massage the joints for her.

As a child JK had continuous hospital admissions once a month.

JK unable to walk not meeting her milestone and was referred to an OT they supplied seating equipment and chair for home and school JK was unable to walk unaided until she was about 11/12 with use of walking frame.

JK has severe behaviour issues that make her hit out at myself and others and self-harm. JK has delayed puberty due to her bone age being at age 12 but has some hormones showing though mixed with the mental age of a 3 year old. This is a nightmare. Once JKs puberty has start doctors have agreed to stop them due to her lack of understanding.

JK had recurring ear, nose and throat problems, and continuing bowel problem plus the incontinence problems managed daily be me.

JK has severe scoliosis of the spine that may need surgery however I have been put on a year waiting list to see this surgeon and will have to go private to see someone sooner.

## **Education**

JK at a young age attended a primary school with one to one support then moved at 8 to middle school at 9 it was decided to try split placement with the middle school and a special needs school this worked really well with one to one support and social interaction with

children. At age 11 JK needed to go to a secondary school we tried a mainstream school for a year however this made her behaviour worse, then she went to full time special needs school.

When JK was 13 it was decided that the school she was in was not helping with JK hyperacusis and would not acknowledge JK has this condition.

### **We relocated to Lancashire for better schools and doctors and specialists 2016**

JK has an Educational health care plan of SEN. However the EHCP has no understanding of the needs of sodium valproate children and don't care about doctors opinions, I have found that teachers in schools and SEN educate every child like every other disabled child not tailored to their specific needs. For example JK mental age is an issue JK school educates her as if she was an autistic however not taking into account JK mental age and her anxiety that contributes to her poor progression yet they are unwilling to listen to parents or professions. As JK has no real need for education as her mental age is so behind her independent skills needs to be focused on, however through many meetings with SEN the objective is education and the money it costs to educate a child.

### **What will JK require for the future as an adult educationally?**

JK requires learning how to be semi- independent, washing, dressing, personal care; she will never ever be alone as an adult as she has no sense of danger.

I have recommended to SEN that JK be placed in a residential school to be independent as possible without me waiting on her as she expects this after so many years, I have been refused by SEN, however the doctors are in agreement but SEN don't care.

JK will have no capability to live independently as an adult, she will never have children never get married and never work.

### **Care**

The care JK was receiving in Cumbria respite 2 nights a month and Mencap 2 nights a week for 3 hours from 2012 -2016

Health services in Cumbria were hit and miss; community nurses gave conflicting information about hyperacusis all wrong. Not one person in the health service had ever heard of sodium valproate syndrome so it was me teaching them.

In Lancashire 2016 I moved here still the same problem nobody has heard of the syndrome so I took it upon myself to research for professionals the particular areas.

The care in Lancashire so far is atrocious. The services have continued to disappoint me by not reading JK EHCP plan not working with me as a parent and take no care and consideration into JK needs that knows more about sodium valproate than anyone else.

I have no respite, I get 3 hours of Barnados a week, the overall care in her school is horrifying and the local authority will not listen no matter how many MPs or authorities you complain to.

### **JK's future care**

She will need supported living or residential home for adults, all depending on if her independent skills improve, support workers and carers.

### **Welfare benefits**

I claim for carer's allowance, disability living allowance, JK will not be able to look after her own money ever in her life so she will needful supervision by me until I can't anymore then my son will have to take over her finances and be a trustee.

## **My personal experience**

### **Health and mental health**

Even before JK was born I had to deal with the emotional effects of losing a twin in pregnancy and then after JK was born the shock, devastation and my world fell apart. The disappointment I felt in the doctor providing the information and of course anger and hurt.

Due to the situation of being a full time carer for a child with challenging behaviour and developmental delay so severe I know suffer from general anxiety, obsessive compulsive disorder (OCD) trust issues when is come to doctors and the local authority, these conditions I have had cognitive behaviour therapy for, however have been that I am unfixable while my life is so wrapped up in JKs world, as I have had to deal with so many traumatic and emotional events during JK life. The frustration of fighting with the local authority and getting support has left me with severe stress which as an epileptic where stress is my trigger is not good.

Due to lifting JK from birth to present my back has built up severe damage. For example lifting JK off the floor from tantrums to lifting wheelchairs, in 2015 I slipped 3 disks in my back which the doctor say was due to years of strain.

JK is physically and emotionally draining.

## **Career and lifestyle**

### **Financial effect**

I can't work due to my commitments to JK this put a strain on the household.

From birth JK has worn nappies and since 9 she has been wearing pull up nappies the cost of nappies and continence pad and huggies pull ups at the moment costs £30 a week. Plus general personal care equipment wipes.

Household alterations that needed to be done to promote her independence at home house, hand rails installed, shower up it for easy access for JK.

Replacement items due to her incontinence, mattresses duvets.  
Hospital costs parking, petrol.

Tantrum cost replacement items, tablets, ipads smashed JK goes through 2 a year.

Safety equipment stairgate for the whole house

Autistic equipment, light weight feeding dishes to aid with her hypermobility

Childcare is not an option as too expensive and residential school is also too expensive even though it would benefit her.

We have a mortgage on our home that is based on me husband wages however without me working we can't provide the right financial backing for the type of house which would help JK progress in her independence

### **Career**

I started having an interest in science growing up and at some point 19/20 I decided that I wanted to become a crime scene investigator I had to delay repeating my GCSES and going to university for a long time until JK operations and hospital admissions had settled down in 2012 I went to university and did a forensic science degree with honours and now have a BSc honours Degree.

However having child with disabilities is not easy when wanting a career, I have no work experience as for 15 year I have been a carer, when I get to interviews I am the only applicant of my age the rest are much younger. Most science jobs are 12 hour shifts and not suitable

hour as I have to be there to get JK up in the morning and put her to bed. At university there was no student finance help for carers so this has left me in debt to student loan company over £36 thousand, if I didn't have JK I could have worked and gone to university.

### **Personal relationships**

My relationship with my son has been damaged by valproate because JK took over my life and still does, (there was no family holidays), I was always in hospital with JK while Alex my son was at his grandads or other relatives. My son has told me that I was a terrible mother to him but a great mother to JK he was 6 when JK was born I live with the fact that having a child with valproate syndrome has broken mine and my sons relationship.

As a parent with a disabled child I found it hard being single mother but I found the strength to keep fighting for my daughter.

I found meeting people and dating was impossible once they found out I had a disabled child they weren't interested, however I was lucky to meet my present husband when JK was 4 however even he had to think whether I was worth getting involved with after he met JK disabled child.

My husband and I at present fall out regularly this is because we don't spend enough time together as we can't find childcare and we can't take JK out for the day due to her noise sensitivity. We don't have holidays or short breaks me and JK have a strong relationship that nobody comes in-between us. JK doesn't like anyone else having her mum's attention which makes things difficult.

### **Support**

I don't have a social life or activities outside of the house.

I have no support from family or friends within the area.

I feel isolated and alone.

Social services next to useless.

### **What effect has having a child with valproate syndrome has on your lifestyle**

My life changed dramatically when I had JK I became a single parent straight away. JK has spent most of her life in hospital from chest infections to operations then as she got older I went to specialists trying to find help for her condition relocating to an area that might provide better specialists.

I have a 21 year old son and my relationship with him is poor because the time I had to put into caring for JK, he was always staying at relatives houses because JK had an operation or

she was ill and I had to stay in hospital with her. My son is honest with me he says that I am a great mother to JK but not so much for him.

It breaks my heart that I have lost my sons love and respect because of something I had no control over.

When I was 22 I had dreams and ambitions to do something with my life, at some point I wanted to go to university and do forensic science and have a rewarding career. Instead I had to wait till 2012 until I could even consider having the time to go to university.

I sum it up my life has no purpose anymore valproate destroyed my life, dreams and my daughter's life. The emotional damage and pain JK and myself has had to suffer is long lasting and will stay with us forever.

I am JK's sole carer from morning to night, I take care of all her personal care duties including pad changing, dressing, showering, washing, brushing teeth.

Valproate has left me isolated and suffering from anxiety myself due to strategic planning constant tantrums.

I worry about her life as an adult and the fact she at 15 has the mental age of a 3-4 year old with no sense of danger in independence skills. Because of the limited information schools have about how to educate sodium valproate children. It seems the local SEN authority just doesn't understand and not willing to listen to parents information.

## **10. AF (Anonymised): Mother's Statement**

I am 38 years old . I was diagnosed with Grand Mal Epilepsy also known as tonic clonic seizures. I was put on Epilim, Sodium Valproate.

In 2004 I fell pregnant, for the first time. I went to see my GP who had no concerns. I went for my 12 week scan, only to be told they couldn't find a heartbeat. My baby had died. At the time I did not know the cause of this could be Sodium Valproate.

Devastated me and my husband tried again. A few months later I found out I was pregnant again. My doctors asked that I speak to a Neurologist this time just to be safe.

In 2005 my son was born. He was born with Myelomeningocele (spina bifida) Hydrocephalus and was diagnosed with Fetal Valproate syndrome. My scans did not detect this. Also I was

told by a leading Neurologist at the John Radcliffe Hospital in Oxford, who contacted me at home. I was reassured by him the dosage I was on, was too low of a dose to cause any harm to my baby.

As a result of this my son was wheelchair bound, unable to talk, could not control his bladder. Was fitted with a V.P shunt and had Epilepsy himself due to countless operations to his head. My life would never be the same again.

My marriage ended due to this. I struggled on my own to bring my son up. In late 2011 he died through a fatal seizure. Eventually his organs shunt down one by one and he went into cardiac arrest. As you can very well appreciate, my life was ruined. I could never be the same woman again.

I now suffer with severe depression. Also a few years ago I endured a nervous breakdown. I still struggle to this day due to all of this. When clearly a change in medication would of prevented this.

Thank you for taking the time to read my statement today.

**11. CD & CH (Anonymised) – Mother’s Statement**

**Pregnancy Outcomes**

Did your baby die during pregnancy?

Yes, with one pregnancy

Pregnancy	Outcome	How many weeks since conception	Year of death
1	Miscarried twins	12 weeks	1986

**Surviving children**

Child 1	
Name (Anonymised)	CD
Year of birth	1987
Does child have an Education Health Care Plan	No

or Statement of SEN	
Will child have full capacity to live independently as an adult?	Yes – currently living independently
<b><u>Services Required</u></b>	
<b>HEALTH</b>	General health ok – has asthma Possible visual characteristics of FVS – wider bridge of nose & has always had memory issues
Operations	Yes but not due to FVS
Therapies	None
Diagnosis	No diagnosis obtained as yet
Prescriptions	Salbutamol for asthma
Assistance aids (glasses, support boots, hearing aids etc)	Glasses, Inhalers
Hospital inpatient admissions	For asthma as a child
What will child require in the future as an adult?	He is now an adult – not services utilised so far
<b>EDUCATION</b>	
Pre-School	Did very well in pre-school – reading & writing before school
School	Started to struggle with memory retention issues especially with exams
Further Education	Despite being very bright – did not achieve potential due to memory retention issues
Other	Has struggled finding the right work due to lack of qualifications & lack of confidence after years of memory/retention/information retention issues
What will child require in the	Parental support - my son now has a daughter and we are

future as an adult?	yet to assess whether there are likely to be any on-going genetic issues
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<b>Child 2</b>	
Name (Anonymised)	CH
Year of birth	1990
Does child have an Education Health Care Plan or Statement of SEN	No
Will child have full capacity to live independently as an adult?	Yes – currently living independently
<b><u>Services required</u></b>	
<b>HEALTH</b>	Has triphalangeal thumbs, extra bones in wrist giving rise to issues with hands, extra bones in both feet with no arch, blind hole at base of spine, possible visual characteristics, wider bridge of nose, curvature of spine
Operations	Advised against corrective operations on hands as a child because she has 'opposition' in both thumbs
Therapies	Some therapy for podiatry issues
Diagnosis	Currently trying to obtain FVS diagnosis
Assistance aids (glasses, support boots, hearing aids etc)	Glasses – has also had orthotics
<b>EDUCATION</b>	
Pre-School	Bright child – reading & writing before school
School	Did well at school
Further Education	Did well with FE – inc obtaining a 2:1 degree
Other	Continuing with on-going education – studying alongside working

What will child require in the future as an adult?	Unknown
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### **Career and Lifestyle**

Are you in paid employment? Yes

What is your occupation? Director of own construction company (with husband)

What is your salary? £18,000

Are you struggling financially? A little

What has been the financial effect of having a child with Valproate syndrome?  
Orthotics, glasses, providing financial support to them as adults (due to lower income)

What effect has having a child with Valproate Syndrome had on your lifestyle?

My lifestyle has been affected because of the effect that FVS has on my, now grown, children; along with the new worry of what effect it may have on my one year old granddaughter.

My children are now living independently but I felt isolated when my children were younger – I was not aware of FVS – I only became aware last November - doctors had always dismissed my concerns stating that I had been ‘unlucky’ in having children affected by Epilim/SV.

My daughter, in particular, has many visible signs of FVS, and this affected her a great deal during her childhood – so much so, that I had to make the decision to remove her from one school due to bullying and place her elsewhere – 15 miles (and a very inconvenient journey) away. She now struggles with walking far due to issues with her feet – at only 28, this is clearly upsetting for her. Her hands are also a very visible and constant reminder of having FVS.

It also affected the choices that my son made in his education; despite being very bright, he has struggled with work – he has never been out of work but, due to a lack of confidence and the ability to retain information, finds it difficult to make career choices. He now has the on-going worry of whether FVS will affect his daughter too.

Personally, having been on SV for nearly 40 years, I have also suffered with the effects of the drug. I have constantly struggled with my weight which has caused a lot of anxiety – I am a

fitness instructor and even exercise has not always helped. I have also had memory (information retention) issues. My anxiety about my memory issues resulted in me making career choices that were definitely below my ability. These memory issues have been getting progressively worse, so much so, that I recently asked my doctor for a blood test, and to check for signs for dementia. I also now have episodes where I lack focus and feel anxious – even though I am a relatively confident person.

## 12. EF (Anonymised) – Mother’s Statement

### Surviving children

Child 1	
Name (Anonymised)	EF
<b><u>Services required</u></b>	
<b>HEALTH</b>	
Operations	1 operations for ears grommets
Therapies	Speech Therapy,. Children and Mental Health Services.
Prescriptions	Ritalin, Methylphenedate
What will child require in the future as an adult?	Support financially as difficult for him to keep a job due to mental health and physical problems.
<b>EDUCATION</b>	

Pre-School	Anger, lower developmental than that of his peers.
School	Struggle all through school ADHD causing lack of concentration right to adult
Further Education	N/A
What will child require in the future as an adult?	Help as unable to keep jobs because of the mental health and his ADHD and impulsivity
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	DLA
Benefits awarded	Declined
What will child require in the future as an adult?	Support with ability to live on own as struggles, has been living in supported accommodation at age of 25. Work support because of mental health and ADHD

### **Career and Lifestyle**

Are you in paid employment?

No

What is your occupation?

Housewife

Are you struggling financially?

Yes

What has been the financial effect of having a child with Valproate syndrome?

I have had to be a stay home mum 24/7 meaning a loss of income, trips to routine appointments and any admissions. I did work right up to 3 month of pregnancy. I had constant calls to schools from pre-school to High School so couldn't work.

Do you have an active social life?

No

Do you have to make special arrangements if you want to go out?

No

Do you have support from friends and family?

No

Do you feel isolated?

Yes

Have your personal relationships been affected by having a child with Valproate Syndrome?

Yes

Are you a single parent?

No

What effect has having a child with Valproate Syndrome had on your lifestyle?

It caused a lot of stress on the family dealing with a child who didn't develop the normal rate having to go to appointments including speech therapy. I ended up with Postnatal Depression because I wasn't getting support, felt isolated and everything just changed.

### 13. GH (Anonymised) – Mother's Statement

Child 1	
Name (Anonymised)	GH
Year of birth	2010
Does child have an Education Health Care Plan or Statement of SEN	We are waiting for him to be assessed again for a Statement he is under the SEN at school which have agreed he needs more help
Will child have full capacity to live independently as an adult?	We can only wait and see he has a lot of struggles in everyday life
<b>HEALTH</b>	
Operations	No
Therapies	speech therapy, physio therapy sound therapy

Diagnosis	<ul style="list-style-type: none"> <li>•global development delay</li> <li>•hypotonia</li> <li>•auditory processing disorder</li> <li>•autistic traits</li> <li>•learning difficulties</li> <li>•low immune system</li> <li>•epicanthic folds</li> <li>•heart murmur</li> <li>•eczema</li> <li>•sensitivities to noise</li> <li>•sleeping problems</li> <li>•coffee latte patches</li> <li>•obsessive behaviour</li> <li>•problems with social skills</li> <li>•problems with balance</li> <li>•problems dressing himself</li> <li>•poor gross motor skills</li> <li>•poor fine motor skills</li> <li>•difficulty's focusing without adult support</li> <li>•difficulty's pronouncing certain letter sounds</li> <li>•muddling up words</li> <li>•limited language and communication skills</li> <li>•difficulty retaining information</li> <li>•difficulty's understanding and using language</li> <li>•long thin upper lip</li> <li>•smooth philtrum</li> <li>•depressed nasal bridge</li> <li>•incontinent</li> </ul>
Prescriptions	Melatonin phenergan
Assistance aids (glasses, support boots, hearing aids etc)	Support boots Glasses
Hospital inpatient admissions	GH was admitted with breathing difficulties at 6 weeks old and again at about 4 months old and again at about 6 months old. He's has been admitted for his eczema at about 12 months old. He has also been admitted several times with recurring croup several times
What will child require in the future as an adult?	Medical, educational, financial support

<b>EDUCATION</b>	
Pre-School	
School	He needs extra funding and a statement so he can get the help he needs
Further Education	
Other	
What will child require in the future as an adult?	

<b>CARE</b>	
Local Authority (council)	
Health services	Speech therapy Medication Physio therapy
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	
Benefits awarded	DLA Middle Rate
Benefits withdrawn	
What will child require in the future as an adult?	Financial support, medical support, education support Employment support

### Career and Lifestyle

Are you in paid employment?

Yes

What is your occupation?

Catering

What is your salary?

£6000 per year

Do you pay into a pension scheme?

No

Are you in receipt of any benefits?

Yes (working and child tax carers)

Do you receive free prescriptions?

Yes

Do you have a Disabled persons bus pass?

No

Do you own your home?

No

Do you rent your home?

Yes (council house)

Have you ever owned your own home?

No

Do you have a mortgage?

No

Do you have any debt?

Yes

Are you struggling financially?

Yes

What has been the financial effect of having a child with Valproate syndrome?

Limited hours I can work now as the strain was too much on my marriage so I am now raising them on my own, need to have a car to get GH around, he still needs nappies, extra costs and time off work to go to appointments.

Do you have an active social life?

No

Do you have to make special arrangements if you want to go out?

Yes

Do you have support from friends and family?

No my family are not local

Do you feel isolated?

Yes

Have your personal relationships been affected by having a child with Valproate Syndrome?

Yes my marriage and friendships and affects my relationship with my other son as GH needs a lot more time

Are you a single parent?

Yes

What effect has having a child with Valproate Syndrome had on your lifestyle?

I have no break I can't pursue a career as caring for him comes first. Hard to make friends as he does not mix well. Struggle going anywhere to noisy. I suffer with anxiety as a result of the guilt I carry for taking the pills and having my world fall apart.

#### **14. HT (Anonymised) – Mother's Statement**

##### **Surviving children**

Child 1	
Name (Anonymised)	HT
Year of birth	1992
Does child have an Education Health Care Plan or Statement of SEN	Did when he was at school
Will child have full capacity to live independently as an adult?	Yes
Services required	
<b>HEALTH</b>	
Operations	2 x Hernia
Therapies	Speech
Diagnosis	Fetal Anti-Convulsant Syndrome
Prescriptions	
Assistance aids (glasses, support boots, hearing aids etc)	Glasses
What will child require in the future as an adult?	
<b>EDUCATION</b>	
School	Mainstream
Further Education	
Other	Extra help
What will child require in the future as an adult?	

<b>CARE</b>	Nothing
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	
Benefits awarded	
Benefits withdrawn	
What will child require in the future as an adult?	A job/career. Daily living help

Child 2	
Name (Anonymised)	HZ
Year of birth	1995
Does child have an Education Health Care Plan or Statement of SEN	Has done
Will child have full capacity to live independently as an adult?	No
Services required	
<b>HEALTH</b>	
Operations	3 x Hernia
Therapies	Speech, occupational behaviour, CBT
Diagnosis	Fetal Anti-Convulsant Syndrome
Prescriptions	Prozac (previously)
Assistance aids	Glasses

(glasses, support boots, hearing aids etc)	
What will child require in the future as an adult?	Guidance, assurance, company, transport, care and assistance
<b>EDUCATION</b>	
School	Special needs
Further Education	
Other	
What will child require in the future as an adult?	Help
<b>CARE</b>	Nothing offered to him
<b>WELFARE BENEFITS</b>	
Benefits you have applied for	PIP & ESA
Benefits awarded	None
Benefits withdrawn	SDA
What will child require in the future as an adult?	Income and daily living help

### **Career and Lifestyle**

Are you in paid employment?

No

What is your occupation?

Housewife

Are you struggling financially?

Yes

What has been the financial effect of having a child with Valproate syndrome?

Expenses – household items, travel to see professionals, extra expenses of education

Do you have an active social life?

No

Do you have to make special arrangements if you want to go out?

Yes

Do you have support from friends and family?

No

Do you feel isolated?

Yes

Have your personal relationships been affected by having a child with Valproate Syndrome?

Sometimes

Are you a single parent?

No

What effect has having a child with Valproate Syndrome had on your lifestyle?

Made my life secluded, no plans can be made. Stress/worry about each day, my son and public issues. Depression. Tension

## **15. IJ & IP (Anonymised) – Mother's Statement**

### **Surviving children**

Name	IJ
Year of birth	1994
Does child have an Education Health Care Plan	No

or Statement of SEN	
Will child have full capacity to live independently as an adult?	Yes
Services required	
<b>HEALTH</b>	
Operations	2 Hernias as a baby.
Therapies	none
Diagnosis	Generalized Epilepsy, psoriasis, constipation other bowel issues, stigmatism, very poor eyesight, tight tendons hands/fingers/ankles/legs. Toe/feet deformities, struggled educationally but never addressed. Anxiety/panic attacks phobias (animals loud noises hospitals dentists)
Prescriptions	Keppra to control epilepsy
Assistance aids (glasses, support boots, hearing aids etc)	Glasses
Hospital inpatient admissions	For two hernia operations
What will child require in the future as an adult?	IJ has shown to cope in adult life, he doesn't allow his epilepsy/anxiety/panic to control him He has a job but struggles when applying for new work as his grades are so low he's often not considered for the role applied for, his prescription's for glasses tend to be costly as he has to have a considerable strength, I cannot foresee how he will be in later adult life, I do understand that although we are lucky that my children are not majorly impacted by Valproate, our journey has been harder due to this as more so IJ had very mild symptoms and had to struggle throughout school and was never noticed as a child needing help.

Name	IP
Year of birth	2000
Does child have an Education Health Care Plan or Statement of SEN	IP HAD a full statement during his latter upper school time, we moved away from our Home in Cornwall to try and get the support IP needed
Will child have full capacity to live independently as an adult?	With guidance Yes
Services required	
<b>HEALTH</b>	
Operations	Minors- teeth extractions. Beads removed that he had pushed into his ears?
Therapies	Previously-speak and language, scallywags (to help with social interaction)
Diagnosis	Short term memory loss, developmental delay, anxiety, stigmatism (glasses needed) photosensitivity, noise intolerance, heart murmur, cross bite jaw (under hospital to have operation- jaw reset) thin lips. Mild facial deformities, hyper-extendable joints, causing the early onset of mild arthritis, dyspraxia, dyslexia, ADD, psoriasis (which flares up during periods of stress anxiety) eczema, toe/feet deformities, does not produce Melatonin so IP struggles with sleep. He is medicated to aid him with a healthy sleep pattern. As a young child IP had a fear of plasters, hospitals, nails being cut, thunder and lightning, dressed up characters, IP was lactose intolerant as a baby/young boy, admitted to hospital for gastric enteritis, had numerous febrile convulsions brought on by severe temperatures. Loose bowels followed by severe constipation (still suffers) IP was at one point five years educationally behind, we tried to get him the help needed in Cornwall but continually struggled.. I attended a FVS conference in London where I approached the main Specialist and asked how can I get help? He advised to move away. So we packed up and

	<p>moved closer to London. It took a while to find a school that had some knowledge of FVS but once IP was at Boswells academy the head of SENCO arranged for him to see an educational psychologist, who then gave IP a full statement of needs and said that Cornwall had in fact failed my son. Again I understand that my children are the milder end of the spectrum but we have had to move mountains to get the help needed, I've fought long and hard. It is often a lot harder to convince the medical professional's that there is something wrong, to prove that I'm not just an over protective mother when children are less affected.</p>
Prescriptions	Melation 10mg
Assistance aids (glasses, support boots, hearing aids etc)	Glasses
Hospital inpatient admissions	Due to go in for jaw operation (Orthognathic surgery) it will be at Queens Hospital Romford
What will child require in the future as an adult?	Again this is something no one has faced, not a lot is known on the impact in later life. But IP will need support guidance with his finances, managing bills and life skills-good decision making
<b>EDUCATION</b>	
What will child require in the future as an adult?	As above we are unsure how his health will pan out. But I anticipate he will still require help with his finances/banking/bills. Also I would imagine arthritis will only get worse as he ages,
<b>CARE</b>	
Local Authority (council)	IP has now passed the age threshold where he had his care plan. Most of the medical team supporting us were paediatric.
<b>WELFARE BENEFITS</b>	
Benefits you have applied	IP was entitled to DLA but since he has turned 16+ it was

for	stopped and IP will not apply on his own merit as with PIP he would have to be sat down interviewed and he starts to panic/ gets anxious and chose to not apply.
Benefits awarded	DLA CARERS
Benefits withdrawn	As above

## Career and Lifestyle

Are you in paid employment?

No

What is your occupation?

Nursery worker (gave up this work in Cornwall to look after IP)

Are you struggling financially?

Yes

What has been the financial effect of having a child with Valproate syndrome?

When IP was receiving DLA I was able to take him on trips/holidays take him swimming which helped his joints,

Do you have an active social life?

We do now. We brought ourselves a little campervan and we all go away in that.

Do you have to make special arrangements if you want to go out?

Previously- when IP was little Yes, I would have to wait until IP was asleep and then go out or He was always with me. He would not leave my side.

Do you have support from friends and family?

Unfortunately not, a lot of people (family included) saw IP as a naughty child, he was a handful, he would frequently meltdown for what others thought was no apparent reasoning- but because I knew him so well I could figure out what was upsetting him. be it the weather forecast, or some TV programme.

Do you feel isolated?

Whilst IP was in his 1-10 year stage YES VERY ALONE- VERY JUDGED , I knew there was something going on with my son- had I been a first time mum, I guess I would have excepted that he was who he was. But he never slept, he was always ill, he was always labelled as the

naughty child, so I often branched away from any formal gatherings for risk of him being the loud, frantic child.

Have your personal relationships been affected by having a child with Valproate Syndrome?

To be honest No, My relationship broke down when IP was one, but it was already on the rocks. I chose to stay on my own for a fair few years to focus on my children, but I have been in a relationship for 8 years now. My partner is adopting IP. My partner has been an amazing part of IP's life and his ability to cope with his challenges, he has taught IP that yes he has a disability BUT his disability does not define him!

Are you a single parent?

During the main growing up period of IP's life 1-11, Yes I was

What effect has having a child with Valproate Syndrome had on your lifestyle?

I felt very isolated and sometimes like I was imagining all I was going through? Initially as a baby he was always poorly, I took him to a nursery group where I was informed that he just wasn't going to settle and wasn't ready for this, tried another one. who after a few visits told me I needed to just walk away and leave him there, they suggested I wait in the park nearby, IP then proceeded to chew the inside of his mouth to the point of bleeding, they called me in and said that it's not in his best interest just yet. And so to pre-school, I had the first initial parent teacher meeting, where It was mentioned IP may have Dyspraxia and then nothing? Until a few years had past and he was showing that he was falling behind dramatically, his teacher approached me and asked had I practised his sight words/ to which I replied yes. she said he had forgotten them all, (first experience of his short term memory loss) We were then referred to The Child and Adolescent Mental Health Team, where I would say I had to fight to prove that IP had difficulties, ( I was asked if I was a drinker? Did I use drugs??? I WAS DISGUSTED as I was a mum begging for help and yet found myself being judged- IP wasn't sleeping, I was trying to hold down a job run a home and seek help for my son) So yes I am angry we still battle each and every day with "YOU LOOK NORMAL" statement, IP will continue to struggle with Maths English and living skills/choices. Our story is far more complex and I have plenty of paperwork to support his struggles. Moving away was a very big struggle (emotionally and financially) but I knew in the long run it would benefit IP (us all to be honest). My mother was diagnosed with terminal lung cancer not long after we left which tore us up as wished to be at home but knew IP wouldn't have had the care plan he had here in Chelmsford. I could type forever as I have left out a lot but I will leave it at this and say

If you need anything further from us I will help in any way possible, (as I still haven't covered- IP having detention's for not understanding French? He couldn't master English?

For pulling faces-It's how he looks? Jaw issues

A supply teacher telling him he will amount to nothing

**16. DM (Anonymised)**

**What age were you when you were prescribed Valproate? 17**

**How often do you have a medication review? 6 monthly**

**What warnings were given to you or your parents? None**

**How long were you taking Valproate before you became pregnant? 5 years**

**How many pregnancies have you had? 10**

**Pregnancy Outcomes**

**Did your baby die during pregnancy?**

**Miscarriage, Termination, Stillborn.**

<b>Pregnancy</b>	<b>Outcome</b>	<b>How many weeks since conception</b>	<b>Year of death</b>
1	Neonatal death	31	2007
2	Medical termination spina bifida	14	2014
3	4 miscarriages		
4			
5			
6			
7			

**Surviving children**

<b>Child 1</b>	
<b>Name (Anonymised)</b>	<b>DS</b>
<b>Year of birth</b>	<b>2009</b>
<b>Does child have an Education Health Care Plan or Statement of SEN</b>	<b>Yes</b>
<b>Will child have full capacity to live independently as an adult?</b>	<b>No</b>
<b>Services required everything</b>	

<b>HEALTH</b>	
<b>Operations</b>	1
<b>Therapies</b>	2
<b>Diagnosis</b>	Sleep disorder, 13 symptoms of fvs, sensory processing disorder, incontinence, anger disorder
<b>Prescriptions</b>	Phenergan
<b>Hospital Consultants</b>	6
<b>What will child require in the future as an adult?</b>	A lot of help
<b>EDUCATION</b>	
<b>School</b>	School
<b>What will child require in the future as an adult?</b>	Social care and sheltered housing
<b>CARE</b>	
<b>Local Authority (council)</b>	Yes
<b>Health services</b>	Yes
<b>WELFARE BENEFITS</b>	
<b>Benefits you have applied for</b>	
<b>Benefits awarded</b>	High care
<b>Benefits withdrawn</b>	

<b>What will child require in the future as an adult?</b>	<b>Yes</b>

**Career and Lifestyle**

**Are you in paid employment? No**

**What is your occupation? Disabled**

**Are you in receipt of any benefits? Yes**

**Do you receive free prescriptions? Yes**

**Do you have a Disabled persons bus pass? Yes**

**Do you own your home? No**

**Do you rent your home? Yes**

**Have you ever owned your own home? No**

**Do you have a mortgage? No**

**Do you have any debt? Yes**

**Are you struggling financially? Yes**

**What has been the financial effect of having a child with Valproate syndrome? A lot of things**

**Do you have an active social life? No**

**Do you have to make special arrangements if you want to go out? No**

**Do you have support from friends and family? No**

**Do you feel isolated? Yes**

**Have your personal relationships been affected by having a child with Valproate Syndrome? Yes**

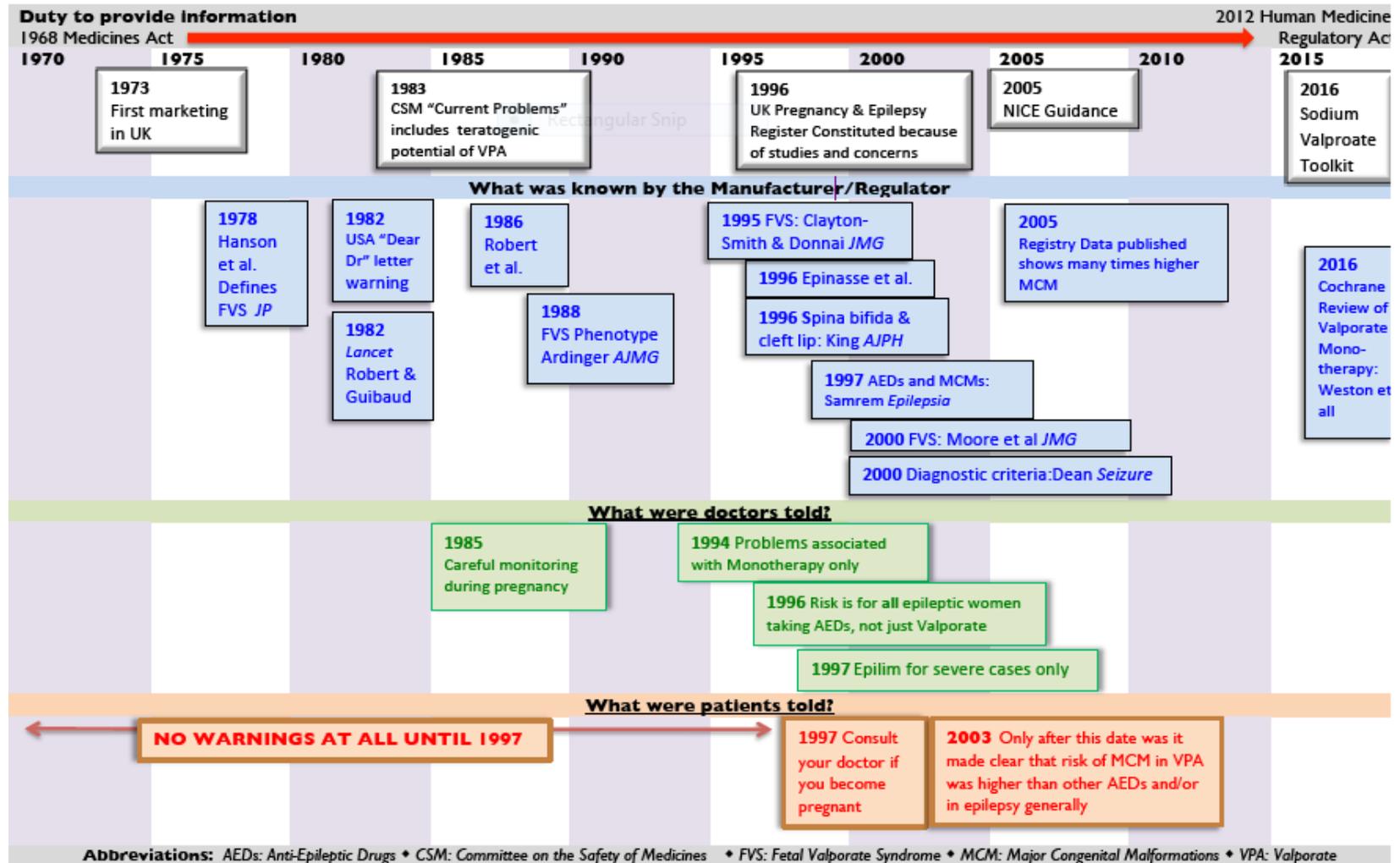
**Are you a single parent? No**

**What effect has having a child with Valproate Syndrome had on your lifestyle? We struggle with everything and family refuse to look after him**

## **APPENDIX B: The 'Information Gap' Infographic**

*A copy of the Infographic inserted below is also provided to the Review as a separate document for ease of reference.*

**Appendix B: FVS: The "Information Gap"**





## APPENDIX C: Licensed forms of Sodium Valproate in the UK

### ***Dispensing types and Formulations***

Sodium Valproate is available in the following formulations<sup>1</sup>;

- **Epilim (Sanofi) (Known as Depakine in France):**
  - Epilim 100mg Crushable Tablets
  - Epilim 400mg Powder and Solvent for solution for injection/infusion
  - Epilim 200 Gastro-resistant tablets
  - Epilim 500 Gastro-resistant tablets
  - Epilim Chrono 200mg
  - Epilim Chrono 300mg
  - Epilim Chrono 500mg
  - Epilim Chronosphere 1000mg
  - Epilim Chronosphere 100mg
  - Epilim Chronosphere 250mg
  - Epilim Chronosphere 500mg
  - Epilim Chronosphere 50mg
  - Epilim Chronosphere 750mg
  - Epilim Liquid
  - Epilim Syrup
  
- **Depakote (Sanofi)**
  - Depakote 250mg Tablets
  - Depakote 500mg Tablets

A number of other manufacturers, beyond Sanofi also produce Sodium Valproate based medications. These are listed below:

#### **Other Manufacturers:**

##### **Zentiva:**

Sodium Valproate Liquid 200mg/5ml

Sodium Valproate 500mg Gastro-resistant Tablets

Sodium Valproate 200mg Gastro-resistant Tablets

##### **Wockhardt UK:**

Sodium Valproate 500mg Gastro-Resistant Tablets

Sodium Valproate 40mg/ml Oral Solution (sugar free)

Sodium Valproate 200mg Gastro-Resistant Tablets

Sodium Valproate 100mg/ml Solution for Injection or Infusion

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<sup>1</sup> <https://www.medicines.org.uk/emc/search?q=epilim>

**Episenta (Desitin Pharma Ltd)**

Episenta 1000mg Pro-longed release Granules

Episenta 150mg Prolonged Release Capsules

Episenta 300mg Pro-longed release capsule

Episenta 500mg Prolonged Release Granules

Episenta solution for injection (Sodium Valproate)

## APPENDIX D: Literature on FVS published Post 2010

### *Additions to citations provided by Professor Peter Turnpenny*

1. Cochrane Database Systematic Reviews
  - a. 'Treatment for epilepsy in pregnancy : neurodevelopmental outcomes in the child' : BROMLEY et al : 2014: Issue 10 : CD 010236
  - b. 'Monotherapy Treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child ' : WESTON et al : 2016 : Issue 11 : CD 0102200
2. Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions. Gentile S. *CNS Spectr.* 2014 Aug;19(4):305-15.
3. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. Smith V, Brown N. *Arch Dis Child Educ Pract Ed.* 2014 Oct;99(5):198
4. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. Veiby G, Daltveit AK, Schjølberg S, Stoltenberg C, Oyen AS, Vollset SE, Engelsen BA, Gilhus NE. *Epilepsia.* 2013 Aug;54(8):1462-72. doi: 10.1111/epi.12226. Epub 2013 Jul 19.
5. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. *JAMA.* 2013 Apr 24;309(16):1696-703. doi: 10.1001/jama.2013.2270.
6. Risks of in utero exposure to valproate. Meador KJ, Loring DW. *JAMA.* 2013 Apr 24;309(16):1730-1. doi: 10.1001/jama.2013.4001
7. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. *Lancet Neurol.* 2013 Mar;12(3):244-52. doi: 10.1016/S1474-4422(12)70323-X.

## APPENDIX E: Alternative AEDS

AED Medication	Indication for Use <sup>2</sup>	Date of first licence in the UK	Teratogenic Potential
Carbamazepine	<ul style="list-style-type: none"> <li>Focal and secondary generalised tonic-clonic seizures, Primary generalised tonic-clonic seizures</li> <li>Trigeminal neuralgia</li> <li>Prophylaxis of bipolar disorder unresponsive to lithium</li> <li>Adjunct in acute alcohol withdrawal</li> <li>Diabetic neuropathy</li> </ul>	1965	<u>Carbamazepine is not associated with an increased risk of developmental delay</u> but is associated with NTD, Hypospadias and heart defects compared to children born to mothers without epilepsy (5.3% vs. 2.3%) <sup>3</sup>
Lamotrigine	<ul style="list-style-type: none"> <li>Monotherapy of focal seizures, Monotherapy of primary and secondary generalised tonic-clonic seizures, Monotherapy of seizures associated with Lennox-Gastaut syndrome</li> <li>Adjunctive therapy of bipolar disorder</li> </ul> <p><i>(Used in both monotherapy and Adjunctive therapy with Sodium Valproate)</i></p>	1990	No significant increased risk of birth defects during pregnancy. Studies show that babies born to women taking lamotrigine, do not have a significantly increased risk of birth defects such as cleft lip, cleft palate or club foot. <sup>4</sup>
Oxcarbazepine	<ul style="list-style-type: none"> <li>Focal seizures with or without secondary generalised tonic-clonic seizures</li> </ul> <p><i>(Used in both monotherapy and Adjunctive therapy with Sodium Valproate)</i></p>	1990	Review of case studies and literature by Montouris 2005 <sup>5</sup> suggests that, compared with the general population, “children born to women receiving oxcarbazepine

<sup>2</sup> <https://bnf.nice.org.uk/drug> - All sources from BNF

<sup>3</sup> Matlow 2012, Is carbamazepine safe to take during pregnancy? Can Fam Physician. 2012 Feb; 58(2): 163–164

<sup>4</sup> <https://www.epilepsysociety.org.uk/news/lamotrigine-no-significant-increase-risk-birth-defects-pregnancy-says-study-08-04-20161#.WqFHRvhLH4w>

<sup>5</sup> Montouris G, 2005 - <https://www.ncbi.nlm.nih.gov/pubmed/15969868>

	<i>therapy)</i>			
	<ul style="list-style-type: none"> <li>• Primary generalised tonic-clonic seizures</li> </ul>			<p><i>monotherapy during pregnancy do not appear to show an increased risk for malformations. However, the number of pregnancies involving maternal exposure to oxcarbazepine identified by this review is not sufficient to draw definitive conclusions.”</i></p>
Gabapentin	<ul style="list-style-type: none"> <li>• Focal seizures with or without secondary generalisation (<i>Used in both monotherapy and Adjunctive therapy</i>)</li> <li>• Peripheral neuropathic pain</li> <li>• Migraine prophylaxis</li> <li>• Menopausal symptoms, particularly hot flushes, in women with breast cancer</li> </ul>	1994		<p>only a small cohort of women (450) have been studied whilst using this drug during pregnancy. Of the babies born to these women, there does not appear to be an increased risk of birth defects in children born to mothers who have taken the drug. There also appears to be no specific birth defect related to this drug<sup>6</sup>.</p>
Topiramate	<ul style="list-style-type: none"> <li>• Generalised tonic-clonic seizures or focal seizures with or without secondary generalisation (<i>Used in both monotherapy and Adjunctive therapy</i>)</li> <li>• Migraine prophylaxis</li> <li>• Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome</li> </ul>	1995		<p>Known to cause Hypospadias and cleft lip/palate<sup>7</sup></p>
Levetiracetam	<ul style="list-style-type: none"> <li>• Focal seizures with or without secondary generalisation (<i>Used in both monotherapy and Adjunctive therapy</i>)</li> <li>• Adjunctive therapy of myoclonic seizures and tonic-clonic seizures</li> </ul>	1999		<p>Has been shown to have a low risk for major congenital malformations to the foetus when taken during pregnancy if used as monotherapy. The risk is higher if used as part of a polytherapy regime<sup>8</sup>.</p>

<sup>6</sup> <http://www.medicinesinpregnancy.org/Medicine--pregnancy/Gabapentin/>

<sup>7</sup> <https://bnf.nice.org.uk/drug/topiramate.html>

<sup>8</sup> Mawhinney, 2013 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3854744/>

## APPENDIX F: A Legal Perspective: The Law and Pharmacovigilance in the UK and EU

### *Relevant Legislation – The Product Liability Directive and the Consumer Protection Act 1987*

Contribution by Marcus Pilgerstorfer: Barrister

Those harmed by medical products who seek recompense in the Courts must either shoulder the burden of establishing fault by the manufacturer and thereby seek to make out a case in negligence, or turn instead to the remedy provided by the Product Liability Directive 85/374/EEC (“the Directive”). The Directive is transposed into national law by Part I of the Consumer Protection Act 1987.

As is well-known, liability under the Product Liability Directive is premised upon damage caused by a defect in a product and it is for the claimant to prove the defect, the damage and the causal relationship between the two (Article 4). The concept of ‘defect’ is defined in Article 6 of the Directive: “A product is defective when it does not provide the safety which a person is entitled to expect, taking all circumstances into account, including: (a) the presentation of the product; (b) the use to which it could reasonably be expected that the product would be put; (c) the time when the product was put into circulation.” At the heart of this concept is the issue of whether a product ‘does not provide the safety which a person is entitled to expect.’ This notion has always been shrouded by a degree of mystery and uncertainty due to its open-textured nature.

At the time the Epilim Litigation concluded in the late 2000s, the number of cases decided under the Directive and Part I CPA was relatively few. The CJEU had considered the substance of the Directive in enforcement proceedings brought by the Commission against the UK: *Commission v UK* (Case C-300/95) [1997] 3 CMLR 923. The issue there was whether the ‘development risk defence’ in Article 7(e) had been properly implemented by the differently (and seemingly more generously) worded s4(1)(e) CPA. The CJEU considered that the differences in wording could be ‘interpreted out’ by national courts when they complied with their duty to interpret the CPA so as to achieve the result of the Directive and gave a firm indication that this should be done.

On the issue of ‘defectiveness’, the main decision at the time was that of the High Court in *A v National Blood Authority* [2001] 3 All ER 289. Burton J distinguished between ‘standard’ and ‘non-standard’ product: “a standard product is one which is and performs as the producer intends. A non-standard product is one which is different, obviously because it is deficient or inferior in terms of safety, from the standard product”. Burton J interpreted Article 6 in such a way so as to require the identification of a ‘harmful characteristic’ in the product (there, the capacity of the blood products to be infected by hepatitis C) before considering whether, in all legally relevant circumstances, the product offered the level of safety that persons were entitled to expect. The product in *A v National Blood* was non-standard: the presence of hepatitis C in some products was not intended. In such a case, Burton J held that an analysis of risk/benefit and avoidability had no place in the defectiveness enquiry and

constituted legally irrelevant considerations. He indicated, however, that the position might be different in a standard product case (which, using Burton J's taxonomy, would describe a product such as Epilim).

More recently, and since the Epilim Litigation, a number of significant jurisprudential developments have occurred in relation to liability under the Directive.

First, in terms of the requirement that the claimant prove that the product is defective, the Court of Appeal has now clarified that this obligation does not require the claimant to prove the mechanism or cause of the defect. This brought the position in England and Wales in line with a number of other European jurisdictions.

Secondly, and more recently, there have been two recent decisions of the CJEU looking – for the first time – at the concept of 'defect': *Boston Scientific GmbH v AOK Sachsen-Anhalt*, and *NW v Sanofi Pasteur MSD*. The first case, the Boston Scientific decision, is a complicated and nuanced one. Suffice it to say here that the CJEU took the position that the particular products concerned (pacemaker and implantable cardiac defibrillator) had an 'abnormal potential for damage' and were defective because they belonged to a group or production series of products which had been shown to have a significantly higher than normal risk of such a fault. The defect standard was thus conceptualised in terms of risk, with the Court not considering it necessary to weigh that risk up against the product's benefits or wide societal utility of the product.

In the Sanofi case, a preliminary reference from France to the CJEU concerning the claim that hepatitis B vaccination gives rise to demyelinating disease, the French judge asked whether Article 4 of the Directive should be interpreted as precluding national judges from assessing causation through presumptions. The decision of the Court focussed mainly on the issue of proof, but the Court did seem to approve the standard referred to in the Boston Scientific decision. In defining what it is necessary for the claimant to show in proving defect in the context of a vaccine case, it was stated that this requires that the vaccine 'causes abnormal and particularly serious damage to the patient who, in the light of the nature and function of the product, is entitled to expect a particularly high level of safety.' From that perspective, the approach in Boston Scientific seems to have been confirmed.

A number of other issues still remain subject to uncertainty, at least at a European level. What is meant by abnormal in this context? What is the relevant reference point? Should the judge compare the safety offered by the product in question with other 'comparator' products? If so, which products are appropriate comparators? Are hypothetical comparator products permitted and if so, how should they be constructed? How is the 'defect' in a product to be defined? Should an assessment of risks and benefits, or the fact a product has received regulatory approval, be included as circumstances that are taken into account when deciding defectiveness?

The latter two points have the potential to be particularly significant in cases of allegedly defective pharmaceuticals. A recent first instance decision in England, *Wilkes v Depuy International Limited* [2017] 3 All ER 589, held (albeit without considering the recent CJEU cases described above) that when the Court is determining defectiveness, a producer could refer to a product's benefits in order to set risks off against them, and also that regulatory approval might also be a relevant factor. Hickinbottom J's conclusion in *Wilkes* as to

risk/benefit contrasts to the opinion of the Advocate General in Sanofi; for the Advocate General, the Article 6 entitled expectations standard “essentially refers to baseline expectations of the product under normal conditions of use. It does not mean that where the product is used normally and causes serious harm in an individual case, that a conclusion of defectiveness necessarily requires a balancing of the costs and benefits of the product.” The Advocate General considered that to take account of the product’s benefits (as well as safety risks) would create “new conditions of liability”. Whilst the Court did not address this point expressly, its application of the defect test to the product before it was consistent with the Advocate General’s views and did not make mention of the benefit or utility of the product (which, as a vaccine, might otherwise have been expected). The relevance of a risk/benefit analysis therefore remains controversial.

Further, the conclusion in Wilkes in relation to regulatory compliance is not universally accepted and may well be linked to the true position as to the relevance of the risk/benefit analysis. It is in tension with the Court of Appeal’s view in Pollard v Tesco [2006] EWCA Civ 393, that the meaning of defect is not given or informed by any cross reference to any other regime (such as, in that case, the British Standard regime). It was held to be a step too far to say that the public were entitled to expect that a product would function in accordance to applicable safety standards. Further, in Boston Scientific, despite noting the presence of the medical devices regulatory regime, neither the Court nor Advocate General indicated that the regulatory assessment was in any way relevant to the findings of defectiveness made. Indeed, the Advocate General made a seemingly opposite observation when contrasting the concept of a “defective product” under the PLD and that of a “dangerous product” for the purposes of product regulation under the General Product Safety Directive 2001/95. He indicated that a “dangerous product” was so defined “independent of the expectations of the public”. For him, it was only the presence of an applicable regulatory scheme that was relevant, because it could heighten safety expectations.

Both issues, amongst others, are currently being considered by the High Court in another first instance decision: Colin Gee & Others v DePuy International Ltd (the Pinnacle Large Head Metal-on-Metal Hip Litigation). Whichever way that judgment goes, these issues ultimately await direct consideration at European level.

It follows from the foregoing that the legal landscape under the Directive has shifted since the Epilim Litigation and still has further to develop.

### *Pharmacovigilance review of Sodium Valproate (Epilim) in Pregnancy*

*Contribution by Dr Peter Feldschreiber*

Since the late 1980s, reports began to describe the developmental toxicity of anti-epileptic drugs, including sodium valproate which related to postnatal dysfunction<sup>1 2</sup>. Although initially these were based on animal toxicity tests, including widespread neuronal death in immature animal brains, clinical evidence of reduced cognitive abilities (e.g. I.Q.) was subsequently described in children exposed to sodium valproate in utero<sup>3 4 5 6</sup>. In particular the Neurodevelopmental Effects of Anti-epileptic drugs (NEAD) study showed that pregnant women with epilepsy monotherapy prescribed valproate between 1994 and 2004 gave birth to children who at 3 years of age had significantly impaired verbal and nonverbal abilities. Six year outcomes indicated that children with fetal valproate exposure continued to exhibit significantly lower IQ than children exposed to carbamazepine, lamotrigine, or phenytoin. In

addition, valproate-exposed children performed more poorly than children exposed to the other three AEDs on measures of linguistic functioning and learning/memory.

In November 2014, the Pharmacovigilance Risk Committee of the CHMP (PRAC) recognised that these data together with more recent studies showed that 30 – 40% of children exposed to valproate in the womb had developmental problems, including delayed walking and talking, memory problems, difficulties with speech and language and lower intellectual ability. There was also evidence of increased risk of autism, and a suggestion that such children were more likely to develop attention hyperactivity disorder.

In addition children born to mothers taking valproate to treat their epilepsy were at approximately 11% risk of malformations at birth such as neural tube defects and cleft palate compared to 2 – 3% risk for children in the general population.

A consequence the CHMP endorsed the recommendations on warnings that doctors should only prescribe valproate if other treatments for epilepsy and bipolar disease were ineffective or not tolerated.

It is difficult to understand why the manufacturers and the regulators delayed in recognising the public health need for warnings regarding these potentially devastating clinical teratogenic adverse events.

The accumulation of adverse events data from 2004 onwards, together with animal toxicology showing impaired neuronal development in animal brains meant that application of the Bradford Hill analysis of causation of adverse events would have been largely satisfied; exposure to rats of valproate resulted in pathological changes in fetal brain development due to the intrinsic pharmacology and chemistry of the drug. Subsequent retrospective clinical data from post marketing safety studies on babies born to mothers exposed to valproate during pregnancy showed that these abnormalities in brain development were reproduced in man.

By 2004 there was sufficient clinical evidence to satisfy the 'Bradford Hill'<sup>7</sup> criteria for the evaluation of causation of these adverse events by exposure to Valproate to allow for serious concern about the benefit risk profile of valproate in pregnancy to justify the implementation of warnings to physicians prescribing the drug. I am therefore of the view that there was sufficient persuasive evidence for the regulatory authorities to warrant a warning of increased risk of valproate induced teratogenicity.

The regulatory authorities (MHRA and EMA) had a duty to ensure the studies were properly evaluated to determine whether an appropriate benefit risk had been assured

Also the manufacturer (Sanofi) had a duty to mitigate the risk to patients by publicizing appropriate warnings, in other words to adopt a precautionary approach to the use of the drug. They had a duty of care to those patients and should have voluntarily promulgated a warning in the patient and product information.

Review of recent studies showing developmental problems in up to 30 to 40% of pre-school children exposed to valproate in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability<sup>8</sup>:

Previous data have shown that children exposed to valproate in the womb are also at

increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).

In addition, children exposed to valproate in the womb are at an approximately 11% risk of malformations at birth (such as neural tube defects and cleft palate) compared with a 2 to 3% risk for children in the general population<sup>9</sup>.

## APPENDIX G – Contributors to this Submission

### *Leigh Day Solicitors*

Leigh Day is a specialist law firm with some of the country's leading personal injury, product liability, clinical negligence, employment and discrimination, international and human rights teams. Unlike other law firms, Leigh Day acts exclusively for claimants who have been injured or treated unlawfully by others.

Leigh Day has a large specialist product liability team with expert knowledge in the area of defective products. The team has gained an enviable reputation for taking on challenging cases relating to medical devices, orthopaedic implants, drugs and other consumer products, and achieving excellent outcomes. As a result, the firm has been ranked No.1 in the field of product liability by the Legal 500 and Chambers & Partners legal directories.

Leigh Day was the lead firm in the high profile metal-on-metal hip litigation which was one of the biggest product liability cases in history. As such, the firm is at the forefront of regulatory and legal developments in the field of product liability and is equipped to handle a wide-range of product liability work.

*"They have an enormous amount of experience and an incredible understanding of product liability litigation. They have a real appreciation of the risks and the best tactics for a case and getting the best outcome for their client."*

- Chambers & partners 2016

*"Leigh Day fields 'an outstanding team of talented individuals', who are at the forefront of group litigation. Bozena Michalowska Howells 'has an excellent understanding of scientific issues' that underpin group actions concerning pharmaceutical and medical devices..."*

- Legal 500 2017

*"I think they are fantastic. If you have a big case against a large corporation and need to push the boundaries, they are the ones you go to."*

-Chambers and Partners 2018

### *Mr David Body*

National Head of Product Liability at Irwin Mitchell LLP until his retirement in April 2015.

Lead Solicitor in the Fetal Anti Convulsant Litigation: 2004 – 2010.

Trusteeships:

- The Thalidomide Trust
- The Patients Association and the Degenerative Encephalopathy Research Group.

*‘He is regarded as a ‘very innovative thinker – he will always find a solution’  
-Chambers and Partners 2015*

*Dr Peter Feldschreiber*

Dr Feldschreiber is dually qualified as a barrister and physician.

Dr Feldschreiber practises from 4 New Square.

Senior Medical Assessor and Special Litigation Co-ordinator to the Commission on Human Medicines, Special Treasury Counsel to Government Legal Service and specialist Advisor to the Faculty of Pharmaceutical Medicine

General Editor : *‘The Law and Regulation of Medicines’* ( OUP )

*Marcus Pilgerstorfer*

Barrister practising from 11 Kings Bench Walk

Specialist in Product Liability Law

*Duncan Fairgrieve*

Barrister practising from 1 Crown Office Row and Avocat at the Paris Bar

Senior Fellow in Comparative Law and Director of the Product Liability Forum,  
British Institute of International and Comparative Law.

Member of the European Commission Expert Group on the European Product Liability Directive

*Professor Peter Turnpenny*

Consultant Clinical Geneticist in the peninsula Clinical Genetics Service (Devon and Cornwall).

Honorary Associate Professor, University of Exeter Medical School

*Dr Rebecca Bromley*

Dr Rebecca Bromley, is a Research Fellow at University of Manchester. For full details of her research and qualifications please see the following link:

<https://www.research.manchester.ac.uk/portal/rebecca.bromley.html>

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## **Footnotes relating to Appendix G**

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<sup>7</sup> . *A generally accepted systematic approach to the problem of causation is the 'Bradford Hill Criteria' ; these are*  
- *strength of association, i.e. the magnitude of the risk ratio;*  
- *consistency of the epidemiological and clinical data showing similar findings in different populations in diverse studies;*  
- *specificity of the effect of exposure;*  
- *temporality of the results of exposure, i.e. that exposure precedes the onset of disease;*

- 
- *biological gradient of the increase in intensity, increase in level and duration of effects of exposure, i.e. a dose response relationship;*
  - *biological plausibility of the hypothesis of causation, i.e. whether there is an association between known biological facts about the pathology of the disease. This is dependent on the state of scientific knowledge at the time the data is being analysed.*
  - *Whether there is a general coherence of theories and evidence of the natural history of the disease and associated exposure.*
  - *are there any objective experimental models to investigate the link between exposure, association and subsequent causality?*
  - *is there any evidence or observations on analogous cases?*

AB Hill 'The Environment and Disease: Association or Causation' (1965) 58 Proceedings of the Royal Society of Medicine 295 - 300

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# FACSaware

1. Please see [Submission from Leigh Day on behalf of OACS Charity and FACSaware](#)
2. [Agenda shared with Norman Lamb MP for meeting 29<sup>th</sup> October 2013](#)

Agenda – Meeting Norman Lamb MP on 29<sup>th</sup> October 2013 – 13.20

\*\*\*\*\*

1. MHRA to issue 'Caution in Use' with Sodium Valproate products and 'Defective' to women of child bearing potential. (this has already occurred in the USA)...<sup>1</sup>
2. MHRA to issue warnings in monthly drug safety update on all medications when Patient Information Leaflet is updated and Evidence based research is published.
3. GPs to recall all patients on SVP and explain safety information and start prescribing alternatives. Men need advice on Fertility, Girls and Women regarding Birth defects and both gender regarding Osteoporosis.
4. Issue statement to all health professionals in hospitals, care homes and community who treat symptoms of FACS in children and adults to enable them to flag up potential patients to be diagnosed.
5. IVF clinics to refuse IVF treatment if the mother taking SVP and advise woman seeks Neurology appointment to discuss alternative treatments.<sup>2</sup>
6. Back Judge Lead Public Inquiry into medicine regulation using EPILIM as case study.<sup>3</sup>
7. Link from Mother's and Father's health and treatments notes to biological offspring notes.<sup>4</sup>
8. Work out cost to taxpayer for damage using estimates supplied by Dr Rebecca Bromley (expert in the field of FACS)<sup>5</sup>. Set costs against Sanofi sponsorship and investment in services, careers, education, universities.
9. Restructure MHRA in line with Public Inquiry findings. Should MHRA be merged with the EMA to save money and improve the consistency of medicine regulation in EU. Neither organisation are working effectively in the best interest of patients, professionals and the taxpayer.
10. Amend Law.<sup>6</sup> Taxpayer should not be paying for damage medical products cause.

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<sup>1</sup> MHRA have confirmed on 14/10/13 that they will issue a statement in the November issue of Drug Safety Update.

<sup>2</sup> Ethics committee to discuss

<sup>3</sup> See Briefing to MPs on Public Inquiry specifications

<sup>4</sup> As per comments by Dr Jim Morrow in BBC Panorama Pills and Pregnancy

<sup>5</sup> Figure estimations

<sup>6</sup> See Journal reports from David Body and Christopher Johnston QC

11. Lobby pharmaceutical companies for Corporate Social Responsibility.
12. HMRC to assess the use of the Patent Box Tax to ensure pharmaceutical companies are using it as it has been intended.<sup>7</sup> 10% tax discount for registering Patent in UK.
13. Dept of Health to provide teaching resources to Dept of Education so that PSHE KS3 and KS4 curriculum regarding Use and Misuse of substances can be taught.<sup>8</sup> Or teratogens to be discussed and taught in Science. Teaching resource is required.
14. Dept of Health to encourage Dept of Education to make teratogen education a compulsory part of the National curriculum.<sup>9</sup>
15. Cases with Significant Wider Public Interest should be funded by Legal Aid. Government needs to be able to override Legal Services Commission decisions in these circumstances.<sup>10</sup>
16. Legal Services Commission should not assess the merits of applications for Judicial Review into their own actions.
17. Money needs to be ringfenced by government for the services people with FACS require.
18. Money to be allocated to Local Authorities to provide education and welfare. This needs to happen immediately to enable services to continue.
19. UK Epilepsy and Pregnancy Register financed by UCB Pharma has significantly differing results when compared with registries outside of the UK.<sup>11</sup>
20. Are there any plans to integrate the data held by the Clinical Practice Research Datalink Group into the UK Epilepsy and Pregnancy Register.
21. Does the UK Epilepsy and Pregnancy Register need to exist?<sup>12</sup>
22. Dept of Health to commission CPRD to investigate AEDs.<sup>13</sup>
23. Dept of Health to support All Trials campaign and to work with the EMA consultation on Clinical Trial Transparency.
24. Dept of Health to issue statement about Clinical Trial Transparency and confirm their position of support or objection with reasons.
25. Dept of Health to improve their communication with the MHRA to ensure that MPs are given accurate information.

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<sup>7</sup> David Gaulke MP and Minister for Tax has full details.

<sup>8</sup> Links provided by Education Minister Elizabeth Truss MP are inadequate.

<sup>9</sup> PSHE education regarding lifestyle choices and Use and Misuse of substances is currently non statutory.

<sup>10</sup> Funding for a Judicial Review into the decision making of the LSC over withdrawal of Legal Aid for FACS Litigation was not granted.

<sup>11</sup> See research review of global registries. This is of major concern as the register is used by government and charities as a reliable resource.

<sup>12</sup> This is a voluntary register that is not publicized by clinicians. Data is not representative of patient group.

<sup>13</sup> Link between biological parents' medical notes and offspring medical notes needs to occur before commencement of research.

If Department of Health do not take these steps it looks corrupt. It is not economically viable to allow the current system to continue and it is not in the best interests of the health of the nation.

\*\*\*\*\*

### **3. Letter between Norman Lamb MP and Alec Shelbrooke MP**



Department  
of Health

From Norman Lamb MP  
Minister of State for Care and Support

Richmond House  
79 Whitehall  
London  
SW1A 2NS

Tel: 020 7210 4850

POC3000829320

Alec Shelbrooke MP  
Chair  
All-Party Group on Thalidomide  
House of Commons  
London  
SW1A 0AA

18 DEC 2013

*Dear Alec,*

I am writing further to our meeting on 29 October when I met with you and Anas Sarwar, and a delegation, to discuss issues associated with Fetal Anti-Convulsant Syndrome (FACS) and the prescribing of anti-epilepsy drugs (AEDs) to pregnant women.

It was tremendously helpful to me to learn first-hand of the personal experiences of Anas' constituent and to hear from the representatives from FACS organisations, all of whom are affected, directly or indirectly, by the use of sodium valproate.

I am pleased to say that, since we met, and as discussed at the meeting, the MHRA have now published their November Drug Safety Update bulletin which contains the article: *Sodium Valproate: Special reminder on risk of neurodevelopmental delay in children following maternal use – not for use in pregnancy unless there is no effective alternative.*

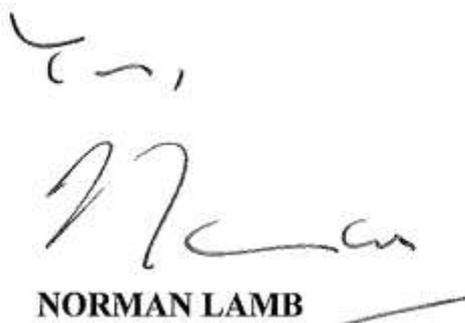
(<http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con336729.pdf>)

The Drug Safety Update bulletin goes to healthcare professionals and aims to promote the safer prescribing of medicines. Internationally, in the light of accruing evidence on the risk of developmental delay in children exposed to valproate during

pregnancy, the MHRA has initiated a Europe-wide review of all the available data on the risks of valproate in pregnancy to see what further measures could be taken to reduce the risk. The review will be led by the MHRA and the Netherlands and is likely to be completed in June 2014. During the review the MHRA will seek advice from UK experts and the views of voluntary organisations and patients groups. I hope that this will reassure those concerned about this issue that the MHRA is doing what it can to raise awareness amongst clinicians with a view to preventing further cases of FACS wherever possible.

In the interim, I have asked my officials to work with the MHRA, and the Royal College of GPs, to consider what further action needs to be taken to ensure appropriate awareness amongst health professions – and in particular prescribing GPs, now that this is no longer specifically referenced in the Quality and Outcomes Framework – of the risks of these drugs, and to ensure women being prescribed them are fully apprised of those risks, and are able to make an informed decision.

I hope this reply is helpful.



**NORMAN LAMB**

**4. Correspondence from Emma Friedmann on behalf of FACT and #FACSaware with the MHRA**

**From:** emma f  
**Sent:** 04 March 2013 15:42  
**To:** drugsafetyupdate,  
**Subject:** Anti Convulsant Medications

To whom it may concern,

I would like to ask you to send out information in your monthly safety updates regarding Anti Convulsant Medications and side effects especially to the fetus when used during pregnancy.

There is substantial research to show teratogenic effects with many anti convulsants and GPs need to be made aware so they can amend their prescribing practice when treating girls/women of childbearing age. GPs do not have time to read all related research and best practice guidelines, but all GP practices print off and read the monthly safety information the MHRA send.

The MHRA could 'Safeguard Public Health' by helping to raise awareness of Fetal Anti Convulsant Syndrome and help prevent years of suffering by the children affected.

Please issue warnings, my Son is disabled for life because I was not informed by my Neurologist and GP of the risks. I would like to have been given information before I chose to become pregnant. The information was there but was not officially publicised. It needs to be officially publicised and you can help.

Information hasn't been given to clinicians when first available therefore patients havn't been informed promptly either. Patient information leaflets have been updated so the pharmaceutical companies have acknowledged the limitations of their products.

Please help the Fetal Anti Convulsant Trust and the Organisation for Anti Convulsant Syndrome raise awareness so that women can make an informed decision.

Thank you

Emma Friedmann



Parent of child with Fetal Valproate Syndrome  
Trustee of Fetal Anti Convulsant Trust

From: drugsafetyupdate  
To: Emma f  
Subject: RE: Anti Convulsant Medications  
Date: Fri, 15 Mar 2013 15:19:12 +0000

Dear Emma,

Thank you for your email regarding information in Drug Safety Update (DSU) on anti-convulsant medicines and side effects, especially to the fetus when used during pregnancy.

We published an article outlining the risks of congenital malformations associated with sodium valproate in 2003 in 'Current Problems in Pharmacovigilance' (the predecessor publication to DSU). The article highlighted that women of child-bearing potential should not be started on sodium valproate without specialist neurological advice, because of the potential teratogenic risk to the fetus (link to the article: <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con007450.pdf>)

There is an increasing amount of research supporting the association of exposure to antiepileptic drugs during pregnancy and an increased risk of birth defects, neurodevelopmental delay and a link

between certain antiepileptics and autism in the child. The current wording in the product information (Summary of Product Characteristics - SPC) available to all prescribers at [www.medicines.org](http://www.medicines.org) outlines the risks to the fetus and the importance of patient counselling prior to any decision to prescribe an antiepileptic to a pregnant woman.

In addition, this same information is contained in the British National Formulary (BNF; an information guide on medicines for health professionals) which is sent to all doctors, and in clinical guidance from the National Institute for Health and Clinical Excellence (NICE) on the management of epilepsy. The patient information leaflet that accompanies the medicine reflects all of the information in the SPC - these are user-tested to ensure that the information is effectively understood and appropriate to the needs of patients.

We continually review the need to issue communications on risks associated with medicines, and carefully consider new information that comes to light and whether further communications are needed. Your feedback will be noted and contribute significantly to our decision-making process.

Thank you for your comments and suggestions.

Best regards,

[REDACTED]

[REDACTED]

**Drug Safety Update**

Vigilance and Risk Management of Medicines  
Medicines and Healthcare products Regulatory Agency (MHRA)  
Floor 3-M  
151 Buckingham Palace Road  
London  
SW1W 9SZ

[REDACTED]

From: [emma f]  
To: drugsafetyupdate  
Subject: FAO: [REDACTED] RE: Anti Convulsant Medications  
Date: Fri, 15 Mar 2013 16:32:32 +0000

Dear [REDACTED],

Is the remit of the MHRA to 'Safeguard Public Health'?

Your warnings are not getting out to patients and their GPs. You (MHRA) have the power to change lives for the better or the worse. I am saddened that you have chosen to change lives for the worse by not issuing further warnings.

Shame on you. I don't know how you can sleep at night.

emma friedmann

From: **emma f**  
Sent: 28 May 2013 14:11:32  
To: drug safety update MHRA  
Bcc:

Dear [REDACTED],

I have asked the MHRA to issue safety updates regarding Sodium Valproate in the monthly bulletin. The MHRA have refused and I can only presume that as editor you are a decision maker. See email below.

As you have a PhD you are presumably intelligent enough to read the links below relating to Sodium Valproate and its use during pregnancy.

There is a 40% risk of birth defects in babies born to mothers taking Sodium Valproate.

Please have a read of this research and highlight to me the papers that the MHRA discard as poor inaccurate research. If you (MHRA) consider all papers accurate please explain to me and the 1000s of parents, carers and people affected by FACS why you refuse to issue warnings.

Thank you

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

<http://www.ptmp.pl/archives/apm/14-1/APM141-9-Jamsheer.pdf>  
<http://www.womensmentalhealth.org/library/psychiatric-disorders-during-pregnancy/obgyn-news-drugs-pregnancy-and-lactation/bipolar-disorder-drugs/>  
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60495-X/abstract#article\\_upsell](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60495-X/abstract#article_upsell)  
[http://jmg.bmj.com/content/39/4/251.abstract?maxtoshow&HITS=10&hits=10&RESULTFORMAT&searchid=1031647228472\\_55&stored\\_search&FIRSTINDEX=0&volume=39&firstpage=251&journalcode=jmedgenet](http://jmg.bmj.com/content/39/4/251.abstract?maxtoshow&HITS=10&hits=10&RESULTFORMAT&searchid=1031647228472_55&stored_search&FIRSTINDEX=0&volume=39&firstpage=251&journalcode=jmedgenet)  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3530733/>  
<http://www2.massgeneral.org/aed/articles/Neurology2005.pdf>  
<http://jmg.bmj.com/content/39/4/245.full> <http://www.annalsofian.org/article.asp?issn=0972-2327%3Byear%3D2008%3Bvolume%3D11%3Bissue%3D1%3Bspage%3D52%3Bepage%3D55%3Baulast%3Dlype>  
<http://jinnp.bmj.com/content/75/11/1575.full>

From: **emma f**  
Sent: 28 May 2013 14:26:41  
To: drug safety update MHRA  
RE: Sodium Valproate - Warnings required regarding teratogenic properties.

READ IT and issue warnings to IMPROVE LIVES AND PREVENT SUFFERING

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672688/>

<http://jnnp.bmj.com/content/75/11/1575.full>

<http://www.annalsofian.org/article.asp?issn=0972-2327%3Byear%3D2008%3Bvolume%3D11%3Bissue%3D1%3Bpage%3D52%3Bepage%3D55%3Baulast%3Dtype>

<http://jmg.bmj.com/content/39/4/245.full>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3530733/>

[http://jmg.bmj.com/content/39/4/251.abstract?maxtoshow&HITS=10&hits=10&RESULTFORMAT&searchid=1031647228472\\_55&stored\\_search&FIRSTINDEX=0&volume=39&firstpage=251&journalcode=jmedgenet](http://jmg.bmj.com/content/39/4/251.abstract?maxtoshow&HITS=10&hits=10&RESULTFORMAT&searchid=1031647228472_55&stored_search&FIRSTINDEX=0&volume=39&firstpage=251&journalcode=jmedgenet)

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60495-X/abstract#article\\_upsell](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60495-X/abstract#article_upsell)

<http://www.womensmentalhealth.org/library/psychiatric-disorders-during-pregnancy/obgyn-news-drugs-pregnancy-and-lactation/bipolar-disorder-drugs/>

<http://www.ptmp.pl/archives/apm/14-1/APM141-9-Jamsheer.pdf>

And the personal panic your lack of warnings is causing women.

<http://www.netmums.com/coffeehouse/pregnancy-64/netmums-52/895371-oh-dear-god-what-have-i-done-taking-epilim-when-pregnant-worse-than-thalidomide.html>

From

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

From: **emma f**  
Sent: 18 June 2013 16:10:47  
To: drug safety update MHRA  
Bcc:

1 attachment (340.0 KB)

Dear [REDACTED],

Attached further information about research done into Fetal Anti Convulsant Syndrome. This has been collated by published researchers in the field.

Please could you issue warnings in the July safety bulletin to clinicians. The FDA in America have been issuing warnings to doctors for years and have recently classified Sodium Valproate as a medication where the benefits do not outweigh the risks to the fetus.

Thank you

Emma Friedmann

From: [emma f]  
To: drugsafetyupdate  
Subject: FW: FAO: [REDACTED]  
Date: Wed, 26 Jun 2013 15:43:22 +0100

Dear [REDACTED],

Hopefully you will have had the opportunity to look at the research on Fetal Anti Convulsant Syndromes. I hope that the Board have agreed that further warnings need to be issued regarding AEDs.

If the Board has not agreed to issue warnings can you advise me who to contact regarding raising awareness of FACS. Please could you also advise me of the MHRA complaints procedure.

Many thanks  
Emma Friedmann

From: [emma f]  
To: drugsafetyupdate  
Subject: Sodium Valproate  
Date: Thu, 12 Sep 2013 12:26:04 +0100

Dear Drug Safety Update Team,

Please could you respond to my enquiry.

You have been contacted by MPs, Healthwatch, me (on behalf of Fetal Anti Convulsant Trust and [www.facsaware.net](http://www.facsaware.net)) and other campaign groups yet you still refuse to issue warnings about the extent and severity of teratogenicity with Sodium Valproate.

I appreciate you had a meeting with Janet Williams and Emma Murphy of INFACT and they have now become Stakeholders but what was achieved by that meeting? The August Drug Safety Update did not include any warning about Sodium Valproate.

What are you doing to raise awareness and communicate risk to doctors so they can inform their patients appropriately. It is the opinion of many that you are failing in your mandated responsibilities. Why is that?

Please respond to me about the research attached below, what was achieved and agreed in the meeting with INFACT and FACSA, when the board is planning to discuss Sodium Valproate use, when a safety warning is likely to be issued and why the delay in responding to me?

Thank you

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

**From:** emma f

**Sent:** 17 September 2013 11:49

**To:** drugsafetyupdate,

**Cc:** healthwatch.co.uk; journal rcgp

**Subject:** FW: Sodium Valproate

Dear Drug Safety Update Team,

I am appalled at your lack of response. I have provided you with all necessary information for you to issue a Caution in Use in your monthly drug safety update.

You are out of touch with current clinical practice by expecting GPs to read and retain all information in the NICE guidelines [2012] and the BNF.

If you have a policy to not issue warnings when NICE and BNF have issued warnings please can you send it to me and I will concentrate my efforts on getting that policy updated by lobbying relevant bodies.

I attach the warning issued by the FDA in USA in June 2013. Why is it that you are unable to issue similar warnings in the UK?

Dr June Raine is perfectly aware of the harm Sodium Valproate (EPILIM) can cause as she sat on the CSM to discuss Valproate in the early 00's.

Other people who are aware and have evaded questions are the speakers at the 5th MHRA Annual Paediatric Seminar on 1st March 2012. I attended this seminar as pharmacovigilance of medication during pregnancy was being discussed. I was hoping that with the continually emerging research about Sodium Valproate and the extent of birth defects that Valproate would be discussed. I was unable to ask Professor Ruth Gilbert or Dr Sarah Mee questions about valproate so I spoke to Dr Sarah Branch who said warnings were not issued regarding Sodium Valproate as it was not seen as defective. At that time the FDA had issued warnings to clinicians that if they prescribe DEPAKOTE to women they should expect litigation.

I agree that Sodium Valproate does not appear to be defective in some populations but the MHRA have a drug safety update that categorises risk ranging from defective to caution in use.

Are you also aware that the PIL accompanying EPILIM mentions male infertility as a possible side effect? Have you demanded further research to find out what EPILIM does to the man to make him infertile? Does it reduce the ability to produce sperm? Does it damage the sperm so they do not reach their destination? If it damages the sperm what happens if a damaged sperm actually fertilises the egg? Is the fetus affected? I know two men who take AEDs and have disabled children. Is it possible for these children's disabilities to have been caused by the medication their fathers took?

If it is not the MHRA's remit to ask such questions and pursue research from the pharmaceutical companies making these medications then whose job is it?

Do you realise how incompetent you as an organisation look?

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

From: **drugsafetyupdate**  
Sent: 24 September 2013 15:20:21  
To: emma f

Dear Ms Friedmann

Thank you for your email concerning the information on the warnings issued by the FDA on the use of sodium valproate in pregnancy. We apologise for any delay in responding to you.

We are indeed aware that the FDA communicated the advice that sodium valproate and related medicines (valproic acid and divalproex sodium) are contraindicated in pregnant women for the prevention of migraine headaches. It is important to note that sodium valproate is not licensed for the prevention of migraine headaches in UK.

It is also important to note that the FDA has not revised its guidance on the use of sodium valproate in pregnant women with epilepsy or bipolar disorder. The FDA advises that in pregnant women with epilepsy and/or bipolar disorder, sodium valproate should only be used in circumstances where other treatments have failed to provide adequate symptom control or are otherwise unacceptable.

We would like to inform you that we are at a national level currently considering the scope for a further review of all the currently available evidence on the safety of sodium valproate during pregnancy and what further regulatory action is required to ensure the balance of benefits and risks is acceptable in patients exposed to valproate. Please be assured that any decisions on the need for further regulatory action will be informed by a thorough and critical assessment of all sources of relevant data. Once the totality of data have been assessed, taking into account national and European expert advice, we aim to communicate to the public the findings of our evaluation and any actions we are taking.

The product information for Epilim mentions an association of Epilim use with male infertility occurring rarely. The exact mechanism has not been fully evaluated in humans but animal model studies show that there are reversible testicular changes and an increased number of abnormal sperm in some rats exposed to sodium valproate. However, the applicability of these findings in animals to what happens in humans is uncertain.

We apologise again for the delay in responding to your concerns and hope that you are reassured to know that we are currently considering the scope of a new review on all available evidence on the benefits and risks of valproate use in pregnancy with a view to taking further regulatory action to safeguard patients if appropriate.

Yours sincerely

, on behalf of the Drug Safety Update team



Vigilance and Risk Management of Medicines  
Medicines and Healthcare products Regulatory Agency  
151 Buckingham Palace Road  
London  
SW1W 9SZ

**From:** emma f  
**Sent:** 26 September 2013 11:55  
**To:** drugsafetyupdate,  
**Cc:** @healthwatch.co.uk; journal rcgp  
**Subject:** RE: Sodium Valproate

Dear [REDACTED],

I am delighted that the MHRA are seeking advice and are going to address whether further regulation is needed regarding Sodium Valproate. A few notes to be added to your considerations.

1. Teenage girls are still being prescribed Sodium Valproate as a first choice treatment for epilepsy.
2. Fertility clinics are still offering NHS funded IVF to women taking SVP without insisting on consultation with Neurologist first to see if other safer medications are suitable for the woman.
3. I am unsure whether further regulation is required, doctors need to be informed by the MHRA in the drug safety update. It's cheap and it's immediate.
4. If abnormal sperm have been observed in tests on rats, what efforts have the MHRA made to collect information on the condition of human sperm?
5. Are the experts you plan to approach for information on SVP published at Cochrane? I have concerns as many 'experts' in Europe still do not accept a link between Neurodevelopmental delay and SVP exposure.
6. Why are clinicians in the USA not prescribing SVP to any women of childbearing potential anymore for any condition?
7. How have the FDA achieved successful communication about the safety precautions associated with SVP and the MHRA and EMA have failed? What can you learn from the FDA?
8. Will research papers and references provided by me be used by the consultation group in their decision making? What information will they use for decision making?

Please can you keep me up to date with progress and advise me when these consultations are due to take place and the timescale for action.

Please could you also advise me of the MHRA complaints procedure as I wrote to you 2 months ago and had no response which lead to the email below being sent.

Many thanks

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust  
Editor of [www.facsaware.net](http://www.facsaware.net)

From: **drugsafetyupdate**  
Sent: 03 October 2013 15:55:56  
To: emma f

Dear Emma

Once again, we sincerely apologise for the prior delay in responding to you. This was an unfortunate oversight on our part and we apologise for the mistake. Please see the following link for further information about how to make a complaint should you wish to do so:  
<http://www.mhra.gov.uk/Contactus/Howtomakeacomplaint/index.htm>.

We will be in touch again by the end of next week with regard to the specific points about sodium valproate that you have raised in your most recent email.

Yours sincerely

A solid black rectangular box used to redact the signature of the sender.

Jon Ashworth MP  
House of Commons  
London  
SW1A 0AA

Dr Ian Hudson  
151 Buckingham Palace Road  
Victoria  
London SW1W 0SZ  
United Kingdom

7 October 2013

Your Ref: JA/rk/05130022

Our Ref: 13325

Dear Mr Ashworth

Thank you for your letter of 16th September on behalf of your constituent Ms Emma Friedmann of [REDACTED] regarding a lack of reply to her query to the MHRA on the 26th June 2013 about the safety of Epilim (sodium valproate) use during pregnancy.

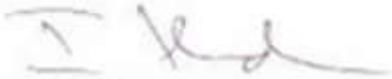
I would like to reassure you that we do take the concerns that Ms Friedmann has raised in all of her correspondence to us very seriously. We replied on the 24th September 2013 to Ms Friedmann directly on the points that she has raised with us up to that date. At the same time, we also apologised for the delay in responding to her letter of the 26th June 2013.

MHRA is currently reviewing all available data on the risks of using sodium valproate during pregnancy, including important new study data produced this year, with the aim of determining what, if any, further regulatory action is needed to ensure the risks of valproate are effectively managed. We will ensure the outcome of the review is communicated to the public including patients and healthcare professionals as soon as possible.

Ms. Friedmann contacted us again on 26<sup>th</sup> September with further questions to which we are currently in the process of responding. We have also provided Ms Friedmann with information about the MHRA complaints procedure on her request.

We hope that our response will provide your constituent with adequate reassurance that we appreciate receiving her views, and are currently taking action to re-evaluate all existing relevant data on the safety of sodium valproate use during pregnancy to decide what further regulatory action may be appropriate to safeguard patient safety.

Yours sincerely,



Dr Ian Hudson  
Chief Executive



From: **drugsafetyupdate**  
Sent: 11 October 2013 17:47:57  
To: 'emma f'

Dear Emma

I am writing to briefly follow up my previous email as I said that we would be in touch by the end of today to respond to your specific points. I just wanted to update you that we are in the process of responding to you on your 8 points and will reply fully early next week.

Yours sincerely

██████████

From: **emma f**  
Sent: 12 October 2013 17:18:02  
To: drug safety update MHRA

Hello ██████████,

Thank you for keeping me informed.

I understand the investigations the MHRA need to do into Sodium Valproate will take some time. I raised this issue with the MHRA in Spring 2012. Since then more babies have been born with these horrific physical and mental birth defects. You could have prevented this but you chose not to.

I would really appreciate if you could send a message out in your monthly drug safety update prompting doctors to read the NICE guidelines and BNF to update their knowledge of epilepsy treatment options and the safety precautions regarding Sodium Valproate. This needs to be done immediately.

Many thanks

Emma Friedmann

From: **emma f**  
Sent: 14 October 2013 16:09:17  
To: MP ashworth, sarwar, shelbrooke ; journal rcgp, healthwatch, healthwatchleics, drug safety update MHRA

The European Medicines Agency is now looking at the use of Sodium Valproate during pregnancy at the request of the MHRA.

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate\\_and\\_related\\_substances/human\\_referral\\_prac\\_000032.jsp&mid=WC0b01ac05805c516f&source=homeMedSearch&category=human](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f&source=homeMedSearch&category=human)

Many thanks for your help in raising this issue.

Emma Friedmann

From: **drugsafetyupdate** You moved this message to its current location  
Sent: 16 October 2013 14:14:22  
To: emma f  
attachment (335.1 KB)

Dear Emma

Please see attached a response to your correspondence from Sept 26, 2013, which raised particular points about sodium valproate.

I hope this information is helpful.

Yours sincerely

, on behalf of the Drug Safety Update team

Oct 16, 2013

Dear Ms. Friedmann

Thank you for your correspondence from 26th September 2013 and 12th October 2013 regarding sodium valproate.

We would like to address each of the points you made to us for our consideration.

1. You have stated that *'teenage girls are still being prescribed Sodium Valproate as a first choice treatment for epilepsy'*. Epilim is currently the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy with or without myoclonus /photosensitivity where there is a clearly positive benefit risk. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.

2. You state that *'fertility clinics are still offering NHS funded IVF to women taking SVP without insisting on consultation with Neurologist first to see if other safer medications are suitable for the woman'*. Regulation of fertility clinic practice is not within the remit of the MHRA although it is expected that those healthcare professionals working within the clinic are complying with regulatory guidance and information in the product information for sodium valproate where it is clearly stated women of childbearing potential should not be started on Epilim without specialist neurological advice.

3. You state that you are *"unsure whether further regulation is required, doctors need to be informed by the MHRA in the drug safety update. It's cheap and it's immediate"*. An article is to be published by the MHRA in the November edition of Drug Safety Update to remind all health professionals of the important current prescribing advice and highlight the initiation of the European review.

4. You asked that *"if abnormal sperm have been observed in tests on rats, what efforts have the MHRA made to collect information on the condition of human sperm?"* All cases of spontaneously reported paternal exposure to sodium valproate in humans are captured and monitored in the MHRA Yellow Card Scheme. Male infertility is already labelled as a possible rare adverse effect associated with sodium valproate exposure in the current Epilim product information for both

patients and healthcare professionals.

5. You asked if *“the experts you plan to approach for information on SVP published at Cochrane? You expressed concerns that “many 'experts' in Europe still do not accept a link between Neurodevelopmental delay and SVP exposure”.* Several experts we have approached for information and advice are very widely published in widely accepted high impact peer reviewed scientific journals The following link provides information on how we seek national expert advice on drug safety issues:

<http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/Pharmacovigilance/index.htm> .

6. You ask *“Why are clinicians in the USA not prescribing SVP to any women of childbearing potential anymore for any condition? In the USA, sodium valproate is licensed for use in several conditions – epilepsy, bipolar disorder and also the prevention of migraine. Sodium valproate is not licensed for migraine prevention in the UK. The FDA has not revised its current guidance on the use of sodium valproate in pregnant women with epilepsy or bipolar disorder. The FDA advises that in pregnant women with epilepsy and/or bipolar disorder, sodium valproate should only be used in circumstances where other treatments have failed to provide adequate symptom control or are otherwise unacceptable. The FDA has issued advice this year that the use of sodium valproate and related medicines are contraindicated in pregnant women when used for the prevention of migraine headaches.*

7. You asked *“How have the FDA achieved successful communication about the safety precautions associated with SVP and the MHRA and EMA have failed? What can you learn from the FDA?”.* We have clarified what the recent FDA communications have been about in the US and would like to reassure you that the outcome of the review in the UK/EU will be communicated as effectively as possible to the relevant healthcare professionals and patients.

8. You asked the following questions: *“Will research papers and references provided by me be used by the consultation group in their decision making? What information will they use for decision making?”* We are extremely appreciative of all of the research papers and references you have provided and we have included several in initial discussions at our national expert advisory group meeting in early October. We will continue to evaluate data that is readily available such as that provided by you in the review and in order to ensure we have the totality of all relevant data included in our evaluation, we have asked for information from all the companies who market sodium valproate in Europe, which may include relevant unpublished data. As you are aware, we are requesting this data from the companies as part of an assessment procedure called an Article 31 European Referral (initiated by the UK on 7th October). This procedure is being coordinated by the European Medicines Agency and further information about it can be found at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/10/news\\_detail\\_001911.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001911.jsp&mid=WC0b01ac058004d5c1)

**From:** emma f

**Sent:** 18 October 2013 14:06

**To:** drugsafetyupdate,

**Subject:** RE: Sodium Valproate

Dear [REDACTED],

Thank you for this full account of MHRA action and opinion.

I am delighted that you are issuing a statement in the November issue of Drug safety update.

I am aware of 15 cases of Clinical Negligence and/or Wrongful Birth being raised by parents against their NHS professionals regarding Sodium Valproate and what it has done to their children. I would urge the MHRA to inform GPs and Neurologists of the increased risk of litigation if they do not follow guidelines set by NICE and BNF.

No win, No fee agreements are being offered by Legal Firms. The Legal Aid reforms have not impacted on the ability of parents to pursue compensation. Can a doctor pursue litigation against the MHRA for not keeping them informed of developing scientific knowledge in this area? If so, Who can the MHRA hold accountable for poor decision making?

FDA warnings.

In spring 2011 the FDA warned clinicians that if they prescribe Sodium Valproate they should expect litigation. I'm sure this was in part a response to the number of litigations being raised in the US about Depakote.

The FDA seem a lot more proactive in ensuring clinicians and patients are kept informed and they seem to understand the wider implications of inaction to patients well being and clinicians professional development and integrity. I have had discussions with psychiatric nurses, obstetricians, general clinicians, healthcare workers and patients in the US who have been aware of the effects of Sodium Valproate for 2 years as they have had government endorsed warnings. These medical professionals are from 5 different States.

I raised my concerns about Sodium Valproate at the 5th Paediatric Seminar on 1st March 2012 and it has taken regular emails, demonstrations and lobbying by parents, MPs, Healthwatch and RCGP for the MHRA to act. In that time it is estimated that another 1000 children have been born with FVS. Even if we half that number (as it's an estimate), it is still a substantial number of children born into a life of vulnerability.

The Yellow Card.

GPs and pharmacists are only using this to report serious side effects. I know this as I have asked quite a few. Other parents with children with FACS have also asked their GPs. This system could be excellent and I would urge you to educate doctors into how to use it effectively and highlight the importance of it.

I have had to change medication doses due to side effects. I still get side effects from Lamotrogine but my doctor does not see the need to report using the yellow card because my side effects are mild.

Parents have tried to self report their Childrens' symptoms of Fetal Valproate Syndrome but couldn't find a way of entering details about a fetus exposed in the womb.

I still think the MHRA should be demanding further research into the abnormal sperm. I know of 2 men on epilepsy medication who have disabled children. Is there a chance their medication could have been the cause? There needs to be more research. The Yellow card could help as could the GP research database. The Yellow Card could be an excellent way to help spot trends but it is not being used to it's full potential.

I truly appreciate your action but there is still a long way to go before the MHRA can claim to 'Safeguard Public Health'.

Please could you confirm that it is acceptable for me to post the attached document online so that interested parties are aware of your action.

Many thanks

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust  
Editor of [www.facsaware.net](http://www.facsaware.net)

**From:** emma f  
**Sent:** 30 October 2013 15:38  
**To:** Chief Executive  
**Subject:** Your ref: JA/rk/05130022 - Sodium Valproate

Dear Dr Hudson,

Yesterday, Tuesday 29th October 2013 campaign groups met with Health Minister Norman Lamb to discuss Sodium Valproate. [REDACTED] at the Department of Health will be working on a project to raise awareness of Fetal Anti Convulsant Syndromes. I presume she will contact the MHRA at some point and your help would be most appreciated.

If the MHRA would like any further information please don't hesitate to contact me.

[REDACTED] can be contacted: XXXXXXXX

I am looking forward to reading the November Drug safety update.

Many thanks

Emma Friedmann

Trustee Fetal Anti Convulsant Trust  
Editor [www.facsaware.net](http://www.facsaware.net)

**From:** Hudson, Dr Ian  
**Sent:** 04 November 2013 08:16:29  
**To:** [emma f]

Thank you for your e-mail of 30 October about your meeting with Norman Lamb and [REDACTED].

[REDACTED] in the Vigilance and Risk Management of Medicines Division of the Agency will be dealing with the European review of the risks of sodium valproate in pregnancy and will be in touch with colleagues in the Department of Health.

Yours sincerely

Dr Ian Hudson  
CEO, MHRA

From: **emma f**  
Sent: 19 November 2013 15:36:43  
To: [REDACTED]@deptofhealth, chief executive mhra  
Bcc:

The film preview was last night and I attach the password and link so that you can watch at a time to suit you. Duration: 26mins. Please do not publish the password.

password:

xxxxxxx

<https://vimeo.com/79741786>

Emma Friedmann

20.11.13

Dear MHRA,

Thank you so much for the prominent positioning of the VPA warnings.

I am full of joy.

There are a few other requests and I hope you will agree their importance to the Health of the Nation.

#### **Wish List**

#### **MHRA to support the amendments to the EU consultation on Clinical Trial Transparency.**

The specific amendments are:

- Amendment 191 which would ensure that clinical trials are registered before they commence.
- Amendment 30 and amendment 250 which say that data in clinical trial reports should not be considered commercially confidential. These amendments would ensure that commercial considerations don't override the interest in public health research.
- Amendment 193 and 253 which would ensure that if a detailed clinical study report is produced about a clinical trial, it should be made publicly available.

#### **MHRA to promote the use of the Yellow Card**

It's a good system and it could work well.

Can effects in a child be linked to the biological parents consumption of pharmaceutical products during pregnancy and prior to conception. e.g If damaged sperm fertilises an egg and the fetus is damaged. Would the Yellow Card pick up that link?

## **MHRA to Safeguard the Public**

You all know you are capable of delivering the goods.

Many thanks

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

From: **MHRA Customer Services**  
Sent: 25 November 2013 09:46:43  
To: emma f

Dear Ms Friedmann,

Thank you for your email which has been referred to our experts for consideration; we will respond to you as soon as possible.

The reference number for your enquiry is **xxxxx**; please quote this number in any future correspondence on this matter.

Our maximum response time is 18 working days, but the vast majority of our enquiries are responded to before this time.

Kind Regards

Customer Services  
External Relations  
Medicines and Healthcare Products Regulatory Agency  
Tel: 020 3080 6000

From: **MHRA Customer Services**  
Sent: 04 December 2013 16:25:50  
To: emma f

Dear Emma Friedmann, Thank you for your email.

The MHRA is fully committed to the amendments to the EU consultation on Clinical Trial Transparency. The Government supports the Commission's proposal for greater transparency under the Clinical Trials Regulation (CTR) which provides a clear legal basis for public access to an EU database, which will include summaries of the results of all clinical trials. We will however seek clarity on what data would be considered commercially confidential in the database to ensure that those sponsors with commercial interests are reassured.

Also, the Yellow Card Scheme would identify any cases where fathers of children report that they have taken the medication and are concerned about the effects on the offspring. These cases would

be followed up for further relevant detail to facilitate a thorough assessment and contribute significantly to the totality of data to be assessed in evaluation of any potential signal of transfer to the child from the male reproductive system in conception. Toxicity of a medication to male fertility is routinely assessed in accordance with standard regulatory guidance for registration of pharmaceuticals for human use."

As the Yellow Card Scheme is a voluntary reporting system it is recognised that continued and sustained efforts to raise awareness and encourage reporting to the Yellow Card Scheme are needed. The MHRA have developed a Yellow Card Strategy which aims to publicise the importance of reporting to the Scheme and raise awareness amongst healthcare professionals and patients. Communication campaign activities undertaken have included display of an information video in GP surgeries, a poster campaign, and distribution of patient Yellow Card leaflets to UK pharmacies and GP surgeries, engaging with healthcare professional bodies, development of a Pharmacovigilance learning module and through working with other organisations to develop training information for healthcare professionals. There are also five regional Yellow Card Centres in the UK who undertake local initiatives to educate healthcare professionals and patients on drug safety and the importance of reporting suspected adverse reactions. The MHRA is also working further to develop links with patient support organisations and health related charities to further support patient reporting of side effects through the Yellow Card Scheme. You may be also interested to know that the next phase of our Yellow Card communications campaign that is being planned is aimed at increasing awareness of the Scheme with healthcare professionals and parents to encourage the reporting of side effects in children.

Kind Regards,

██████████

Customer Services  
External Relations  
Medicines and Healthcare Products Regulatory Agency  
Tel: 020 3080 6000

From: **emma f**  
Sent: 05 December 2013 16:54:42  
To: MHRA info, drug safetyupdate, chief exec, ██████████, Sarwar, Shelbrooke, Ashworth MP,  
Cc:  
Bcc:

Dear MHRA,

Thank you for your response.

I am glad you are pursuing the promotion of the Yellow Card Scheme. There is still a lot you need to do as doctors, pharmacists, nurses and therapists I have spoken to are either not aware of the scheme or will only report life threatening e.g anaphylactic shock, adverse reactions.

The Nursing Times published a good article in November about the Yellow Card and hopefully more nursing staff are now able to complete it on behalf of themselves and their patients.

I have just completed the yellow card online for my Son who has Fetal Valproate Syndrome and despite my previous requests for you to amend your database to include fetal exposure you have not.

My Son did not take the tablets - his Mother did. My Son had the drug intravenously and not prescribed for a health condition he was suffering from. I've selected tablets but that's not an accurate description of my Son's exposure.

I had also typed a detail incorrectly and went back to amend it. It did not amend so you have incorrect dates for my Son's exposure to this medication.

I included my telephone number, it wouldn't accept it as I hadn't put in an extension number, I don't have an extension number so I added a zero, so you have an incorrect telephone number for me (the reporter/carer).

There are also medications that have been shown to affect subsequent generations e.g DES. There is no facility to report that a harmed individual's Grandmother took a medication while pregnant.

Obviously a bit more work required on the online form.

Maybe while you get it updated you could save time and money and add the Father's medicine consumption to the form so that observational data and possible trends can be collated regarding medicines effects on the male reproductive system and child, as you agree the Yellow Card could handle that type of data. A facility to report what medications your Grandparents and Great Grandparents took during the conception process would also benefit the consumer and add to developing scientific knowledge.

Dr Dan Poulter MP said in response to a question by Alec Shelbrooke MP a few weeks ago that there was a link between a Mother's medical notes and their biological offspring. If this is correct then it seems very odd that the MHRA who are heavily involved in the implementation of the Clinical Practice Research Datalink Group have not created the link in the Yellow Card system. Maybe you could start working together with a co-ordinated efficient approach.

Regarding the clinical trial transparency issue. You state "We will however seek clarity on what data would be considered commercially confidential in the database to ensure that those sponsors with commercial interests are reassured".

Thank you for your honesty but - You exist in your jobs to SAFEGUARD THE PUBLIC not to REASSURE SPONSORS WITH COMMERCIAL INTEREST.

If you (the MHRA), are being prevented from safeguarding the public due to sponsors with commercial interest may be it's time someone blew the whistle so that we have safe medicines in the UK. Maybe that's an issue for the ethics committee.

I hope the #facsaware team and associated organisations can help to publicise the Yellow Card system. I hope we will also be able to highlight the reasons why you may not be able to fulfil your mandated role in safeguarding the public and ensuring clinical trial transparency to improve patient safety and the advancement of innovation and development within medical sciences.

FACSAware will publicise the Yellow Card when the online form is fit for purpose. Please can you let me know when the online form has been updated so we can publicise it.

Please could you also confirm that I can publish the communications I have with the MHRA online to share with interested parties.

Many thanks

Emma Friedmann

Trustee of Fetal Anti Convulsant Trust

From: **MHRA Customer Services**  
Sent: 09 December 2013 11:46:12  
To: 'emma f'

Thank you for your email which has been referred to our experts for consideration; we will respond to you as soon as possible.

The reference number for your enquiry is xxxxx; please quote this number in any future correspondence on this matter.

Our maximum response time is 18 working days, but the vast majority of our enquiries are responded to before this time.

Kind Regards

[REDACTED]

Customer Services  
External Relations  
Medicines and Healthcare Products Regulatory Agency  
Tel: [REDACTED]

From: **MHRA Customer Services**  
Sent: 20 December 2013 15:21:26  
To: emma f

Dear Ms Friedmann,

Thank you for completing an online Yellow Card form for your son. Please accept our apologies for the difficulties you had completing the form for your son's case; however, we can confirm the information on our system has been updated to reflect the information provided in your email correspondence.

We are grateful for the points you raise for possible changes to the online Yellow Card for reporting Adverse Drug reactions (ADRs) occurring during pregnancy, we are always keen to hear from users as to how the system can be improved and we can confirm that we are currently working on introducing a number of changes to ensure more information is gathered for these types of reports. Currently you will be aware that when the patient is entered as a female aged 16 years or above an additional field appears to ask whether the patient is pregnant and if so the date of the last menstrual period. In addition to this we are planning to add further questions to include expected date of delivery, information on previous pregnancies, dates of ultrasound scans and any findings and whether the patient has started or stopped any medications during pregnancy. We are also planning to publish an article in our Drug Safety Update bulletin highlighting these changes to the online Yellow Card form.

When capturing information on medication that a parent and or grandparent has taken on the online Yellow Card, this information should be reported in the field for 'Other information you think may be important' or the 'additional information' section on the paper Yellow Card. We will also be updating the text on the website form to explain how this information should be populated and are developing a guidance document which provides more detailed advice on how to complete a Yellow Card for an ADR following a mother, father or grandparent taking a medicine.

The Yellow Card form is used to collect information on a range of adverse drug reaction reports and when creating the online Yellow Card it was important to balance the need to capture as much information as possible without putting people off reporting due to the length of the form. This was carefully considered when the online Yellow Card form was originally developed when it was put it through a series of pilots to test usability. Feedback from members of the public was used to update the form to ensure it was user friendly and fit for purpose.

Every Yellow Card report we receive is individually reviewed and we assess what other important information would be helpful for that individual Yellow Card. With this in mind the team at the MHRA request follow-up information for Yellow Cards to ask more detailed and specific questions to aid the assessment of a case. For ADRs occurring during pregnancy these follow-up requests would routinely include relevant peri natal information such as any delivery complications and details of the new born including any birth defects or developmental concerns

With regards to your concerns over the transparency of clinical trials, whilst we will ensure commercially sensitive data is protected this is not at the cost of safeguarding the public and ensuring the robustness of regulatory action we undertake to protect public health.

Thank you for your support of the Yellow Card Scheme.

Kind Regards,

[REDACTED]

Customer Services

External Relations

Medicines and Healthcare Products Regulatory Agency

Tel: [REDACTED]

22/12/2013

Customer service questionnaire completed.

I said I am 'Satisfied' with the Customer Services Team and gave the following comments on the service and how it could be improved.

When dialogue is started between a customer and the MHRA it would be nice to have one point of contact in the MHRA customer services team. I am unsure whether the people I emailed in the Spring are aware of the email I sent last month. Point of Contact resolution can be assessed when one point of contact responds to the customer.

Responses are usually within the 18 days.

It would be nice if my complaint about being ignored for 3 months would have been passed straight

away to the complaints team rather than me having to contact and raise the issue with my MP. Then me having to contact the complaints department as well.

General politeness, grammar and spelling is good.

I am not impressed by the MHRA as a whole as there appears to be conflict of interest that looks corrupt. It should not take 2 years for warnings to be issued about the safety of a medication that causes severe lifelong harm to 500 people per year, causes immense suffering, puts doctors at risk of litigation and costs the taxpayer £Billions. The only group who benefit from this are the pharmaceutical companies and their employees and shareholders.

Customer services appear to be the only department that is working adequately.

Thank you.

From: **emma f**  
Sent: 22 December 2013 12:20:58  
To: MHRA info

I have just filled in the Customer Services Survey you sent me in the link below. I am unsure whether the form has been submitted as I received no 'your form has been received' statement when I had clicked 'done'.

Here is what I wrote.

\*\*\*\*\*

'Satisfied'

When dialogue is started between a customer and the MHRA it would be nice to have one point of contact in the MHRA customer services team. I am unsure whether the people I emailed in the Spring are aware of the email I sent last month. Point of Contact resolution can be assessed when one point of contact responds to the customer.

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Customer services appear to be the only department that is working adequately.

Thank you.

\*\*\*\*\*

Is the survey submission working? Will my data be included in your research or has it gone missing?  
Your IT systems are letting down Customer Services and the effectiveness of your projects (Yellow Card).

Have a lovely Christmas and best wishes for the New Year.

Emma Friedmann

From: **MHRA Customer Services**  
Sent: 22 December 2013 12:21:06  
To: emma f

[MHRA autoresponse]

## 5. Valproate Report dated 01.07.14

# Valproate

Report by FACSaware  
Compiled by Emma Friedmann

FACSaware is an awareness project set up by the Fetal Anti Convulsant Trust

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## Current Information provided by Healthcare professionals

- Patient told there is a small risk of birth defect – under 10%.

## Information Source

- EMIS Guidance
- UK Epilepsy Pregnancy Register
- Epilepsy Society website

MHRA have issued updates quoting research studies that have shown a 35-40% risk.

Drug Safety Update, Volume 7, Issue 4, November 2013.

MHRA have not mentioned that risk % in the summary text, but by issuing the references to the research documents they are endorsing the findings. Doctors do not have enough time in a 10 minute consultation with a patient to read 5 research documents.

## What discussions/information should be shared?

Nothing should be kept secret from the patient. Clinicians need to enable their patients to make an informed choice.

## At start of treatment (Valproate should be used as a last resort)

- This medication is not suitable if you wish to have a child in the future.
- We use this as a last resort when other medications are not effective or tolerated.
- It causes Birth Defects in ..% of babies exposed.
- Many children remain vulnerable with physical and learning disabilities for the rest of their lives and need 24/7 care to keep them safe.
- How do you feel about being a carer for the rest of your life?
- How will being a full time Carer affect your future career aspirations and lifestyle?
- Sterilisation to be offered.
- The rights of the child should take priority over the desires of the woman to have biological offspring. Patients should be encouraged to think about this ethical dilemma in a balanced way.
- You don't have to become pregnant to be a parent.

## During Pregnancy

- All staff involved to be aware of FACS and be able to answer questions from parents.
- Terminations to be available to 20 weeks.
- Regular screening and in depth support and discussion if abnormalities are noted so that an informed decision about whether to have a termination can be made.
- All pregnancies exposed should be highlighted in the care data of the woman regardless of outcome. Termination, miscarriage, still birth, neonatal death.

## During Delivery

- All staff to be aware of FACS and likely complications.
- Hospital birth recommended.
- Epidural encouraged for the safety of the baby and mother. So that if mother has seizure or baby is in distress emergency caesarean can be performed with greater ease.
- Explanation to parents that Baby will need to be taken to NICU for monitoring.

## After Birth

- Baby taken to NICU for monitoring.
- Umbilical cord to be used for research. (Project in Nottingham asking for donors).
- Health visitor to visit the home once a week for at least 6 months. Compulsory for child protection purposes and maternal health and wellbeing.
- 6 monthly appointments with Paediatrician until school age.
- Paediatrician to contribute to Statement of Special Educational Needs. Now EHC plan in UK.

## Early Years Foundation Stage

- Educational requirements letter to be made available to playgroup and teaching staff.
- School SENCO to cooperate with parents to ensure consistency and to work out a plan that suits the family and their lifestyle.
- School to understand child isn't necessarily being naughty, they may have behavioural disabilities or sensitive hearing and require additional 1-1 support.
- School to contribute to Yellow Card reporting system.
- Educational Psychologist to be available to the school.

## Key stage 1 and 2

- Child to be supervised closely or from a distance to ensure they are not being coerced by other children to be naughty (due to their vulnerability) or being bullied.
- Parents to be given a double length parents evening consultation.
- Children to be kept back a year if necessary, unless this disrupts friendships.
- Paediatrician appointment to monitor progress and difficulties.
- Paediatrician to report back to EHC Plan to ensure adequate services are made available.

## Key stage 3 and 4

- Puberty, consent, morals to be discussed in small groups to enable independence and social acceptance in adulthood.
- Skills to be noted and extra resources given to enhancing those skills – IT, Music, Art, Memorising facts, obsession for perfection.
- Staff to monitor for signs of bullying.
- Staff to refer to mental health service teams.
- Behavioural Therapies to be tried before medication.
- Paediatrician appointment at transition age with report sent to PIP assessment team.
- Consultation with child support teams and adult support teams to ensure consistency and understanding.

## Family support

- Visits from Health visitor to include safety information for women with uncontrolled epilepsy. Use of stair gates, playpens, alarm systems.
- All health problems to be dealt with promptly.
- Doctors and other professionals to believe that FACS exists and not to ridicule the parents for their concerns.
- Proactive management of family wellbeing.
- Respite offered.
- Sibling activities and support offered.
- Counselling and mental health service provision for parents.
- Accessible community facilities.
- Free legal advice and representation.
- Welfare payment decision teams to know what FACS is.

## Adulthood

- More residential care provision for people with Learning disability. Near to their family support network (Parents, Siblings, Cousins and community).
- More understanding of the differences between Mental Health illness and Learning Disability. Specifically regarding Innocence. Patients with Mental Health illness often do not trust those who are looking after them, and many have been sexually active. People with Learning disability have grown up with a carer who they have trusted to keep them safe and generally have not been sexually active. Police, Prisons, Hospitals, Care homes, Community centres need to provide for this difference.
- Recreational activities available for adults with FACS.
- Continuing educational activities to further develop the mind and prevent mental health conditions associated with behavioural disorders and isolation.
- Advocacy service.
- Monitoring for signs of abuse, neglect, malnourishment and poor health.
- Monitoring for signs that adult with FACS is being abusive.
- Monitoring for signs of addiction.
- Families to be listened to.
- 5 yearly specialist appointments with medical clinician.

## Who should provide information?

- GP at 6 monthly medication review appointments. NICE Guidelines 2012 recommend annual appointments with generalist or specialist as a minimum for women with epilepsy.
- GP to give woman booklet of general FACS info with further reading list including alternative parenting options and disability services provision.
- GP to discuss risk of defect.
- Woman to sign to say she has had risk explained by GP or specialist.
- School to educate all children about Teratogens and products that may damage sperm – KS3 and KS4
- Teachers to have access to government endorsed resources that include medicines of concern and accurate risk statistics.
- Teachers to send relevant information to the girl's parents in envelope to home address to prevent bullying in school.

## Ways to provide information

- 8 page booklet with clear language. With emphasis on Informed Choice.
- A symbol on the outside of the medication box for women with poor literacy levels and as a subconscious reminder every day that pregnancy is not advised and should be avoided. Pregnant woman in a circle with strike through.
- Black triangle for pharmacists on outside of box.
- Warning system on computer databases used for prescribing.
- EMA to provide patient user friendly summary of side effects including risk % on website.

## What is needed to increase awareness among women?

- Women not to be prescribed Valproate in the first instance.
- Women to have a full explanation of all ADRs at their 6 – 12 monthly medication review with their doctor.
- All Valproate products to have bold, prominently placed symbols on the outside of the box.
- Risk statistics obtained from evidence based research to be printed prominently on Patient Information Leaflet. E.g 35% or 2 in 5 babies exposed.
- Women to sign that they understand the risk when collecting their medication from the pharmacy.
- Women to sign that they understand the risk when receiving advice from their clinician.

## Other issues.

The Rights of a Child to have a quality of life free from unnecessary suffering and vulnerability should take priority over a woman's right to become pregnant and give birth to a child.

I believe that Valproate products should only be prescribed to women of childbearing potential in a country if the country commits to provide quality care, education and welfare to those affected by the teratogenic side effects. Unplanned pregnancies will always happen.

FACSAware would like Valproate to be banned for use in pregnancy for all conditions.

Pharmaceutical companies should be granted a license for a product only when they contribute towards the cost of looking after those affected by their products' ADRs and for that additional cost not to be passed on as a price increase. Example: 40% have additional needs requiring an extra £1million from the state. How many prescriptions, how many pregnancies, how many affected, multiply by £1Million and that is the contribution the pharma company has to make each year to the cost of their care if they want to continue selling their product to that patient group.

If they don't pay for the cost of side effects, they don't get permission to market the product and the product will not be endorsed by the health department of the country.

Licences granted by regulators to be issued when a pharma company acknowledges the limitations of its product and agrees that the medication 'causes' the side effects that are warned about in the information leaflet.

EMA to press WHO to recognise FACS and that there is a syndrome specifically related to Valproate

exposure. Doctors will not diagnose, refer for diagnosis or complete Yellow Card (reporting system) without acknowledgement by WHO and National Guidelines on the recommended treatment of the syndrome.

Doctors to be given up to date information in line with developing scientific knowledge to enable them to make informed prescribing choices and protect them from litigation claims.

Valproate has been shown to cause abnormal sperm in rats. PIL in Epilim states male infertility as a side effect. MHRA has confirmed this is due to the abnormal sperm. What happens if abnormal sperm fertilise egg? I know 2 men who took AEDs during conception and they have disabled children with Neurodevelopmental and physical defects from birth. More research is required in this area and could be done using observational research data if there was a link between the father's medical notes and that of his biological offspring.

Epilepsy and pregnancy registers need to be consistent across the continent (preferably globally) to allow statistics from different genetic groups to be compared with each other. Valproate and other AEDs may be safe in some populations. We don't know and trends cannot be noted as the Epilepsy registers run for differing amounts of time and collect different information.

Registers used for governmental statistics and information sources for professionals could be a lot better. The EU and its member states have the ability to make it better.

Prevent Suffering and Improve Lives.

## Contact Details

FACSAware Campaign Director: Emma Friedmann



www.facsaware.net



<https://www.facebook.com/groups/438098456270635/>



FACS campaigners with Alec Shelbrooke MP after APPG on 18<sup>th</sup> June 2014



FACS campaigners outside the MHRA on 2nd August 2013

## 6. Valproate: Roles and Responsibilities

Report by FACSaware

Written by Emma Friedmann

Date: 12th March 2015

### Roles and Responsibilities

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### MHRA

- Issue reminders in drug safety update

- Use consistent language to ensure clarity. 2-3 times more likely, 10%, 1 in 10, 10 in a 100.
- Proactively regulate to prevent harm, safeguard the public and educate clinicians.
- Ensure Public Health England and Local Authorities receive selected drug safety updates.
- Operate transparently to build trust in UK regulation.

I don't like the expression 'up to 30-40%' as it is not as cautious as saying '30-40% are affected' or '40% have birth defects'. I have raised this and appreciate the MHRA work within strict guidelines so cannot necessarily alter their wording.

Yellow Card. The MHRA need to promote the use of the Yellow Card in Health, Education and Care settings. Fetal exposure to drugs can now be reported using the Yellow Card. I haven't tested whether the changes made to the online form work yet but am pleased the MHRA have made this amendment. Professionals need to receive training in how to complete this for children suspected of being affected by a pharmaceutical teratogen. Health visitors, preschool SEN teachers, Educational Psychologists, SENCO (in mainstream schools), speech therapists, physiotherapists, CAMHS and occupational therapists are probably the most suitable group to report suspected cases of Valproate syndrome as the neurodevelopmental delay will be able to be explained in more detail by a specialist rather than a GP or hospital consultant.

## Department of Health

- Continue to update NHS choices information.
- Continue to work with medical colleges and associations to work out and implement effective dissemination of information.
- Raise areas of concern requiring policy amendments with Secretary of State for Health.
- Highlight budgetary requirements to Secretary of State for Health.

Pharmacists have not received updates on their IT systems yet to give warning of issuing valproate prescriptions and automatically print a statement of risk on the label when dispatched to patient.

Alison Beedie at the Dept of Health has confirmed that warnings will pop up on pharmacy IT systems when the systems are updated and that she is having talks with pharmacy teams on how to ensure pharmacists are aware and what their role should be.

## NICE

- Develop guidelines for the treatment of FACS.
- Update guidelines for epilepsy and mental health treatment.
- Develop guidance for PHE to use in the Local Authority setting.

NICE guidelines state people with epilepsy should be seen at least annually by a generalist or specialist. I have 6 monthly medication reviews with my GP and know that at that meeting would be a good time to discuss safety data and implications for family planning.

Patient / Doctor discussion on risk/benefit of valproate and contraception should be noted on the patient's medical records and consent should be obtained by the patient that they understand the implications of using valproate while pregnant. It may be beneficial for legal purposes for the patient to sign a consent form and for that form to be scanned onto their medical records and filed. A consent form protects prescribers from Litigation and enables the child to Sue their mother for the disabilities her decision has caused.

I have never challenged my GP or Neurologist. They are the professional. They make clinical decisions and manage budgets. I have had good chats with nurses, health visitors, teachers, youth and social workers and they are the people who should discuss the wider implications of childlessness, relationships, having a child with SEN and being unable to follow a career due to care commitments. Support needs to be available and an holistic approach would enable girls and women to make an informed choice about their future.

## Pharmacists

There has been mention that pharmacists could advise on contraception for women taking valproate. I feel this is not suitable, I do think it appropriate for pharmacists to highlight the importance of reading the patient information leaflet and having some copies of the MHRA patient information distributed by the Central Alerting System. Advice needs to be given by a doctor known to the patient in a confidential and documented environment. A pharmacist cannot provide this environment.

## Public Health England

- Act upon drug safety updates from MHRA.
- Put in place dissemination of information practices based on the locality of Local Authority.
- Department of Health Social Care blog to be issued by PHE to LAs.

I attended Local Offer Live in Leicester in January. There were displays from all education, healthcare and social care providers and services in Leicester. I was there in my capacity of School Governor of a SEN school and also as a parent of a child with valproate syndrome. I discussed with some youth workers whether they knew about valproate and the risks. They hadn't heard of risks but support teenage girls with Mental Health illness and epilepsy. Their position in raising awareness is very important. Girls will speak to their support worker about personal issues that they cannot discuss with their family and do not feel comfortable about talking about with their doctor. I raised this with Alison Beedie and the following week the Social Care blog was updated with plain easy language and links to MHRA warnings and patient advice. It would be beneficial for this Social Care blog to be disseminated to Local Authorities Social services departments, charitable and non profit activity and support groups and businesses who provide support.

Yellow Card. The MHRA need to promote the use of the Yellow Card in Health, Education and Care settings. Fetal exposure to drugs can now be reported using the Yellow Card. I haven't tested whether the changes made to the online form work yet but am pleased the MHRA have made this amendment. Professionals need to receive training in how to complete this for children suspected of being affected by a pharmaceutical teratogen. Health visitors, preschool SEN teachers, Educational Psychologists, SENCO (in mainstream schools), speech therapists, physiotherapists, CAMHS and

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Alternative parenting options. I would like the emphasis for women dependant on Valproate to encourage looking at Fostering, adoption and surrogacy. These women will need to be supported emotionally through this process. I'm not sure who should deliver this but the Specialist Epilepsy nurses would be well placed and could signpost patients to the Local Authority teams. Family planning clinics could also give more specialist advice upon referral from an Epilepsy Nurse, GP or Neurologist.

## Healthwatch

- Raise awareness in communities.
- Signpost to further information and support.

Healthwatch could do a great deal in promoting better understanding in communities of Mental Health illness and Epilepsy. Information could be made available to communities so there is better understanding of what it's like to live with a condition that has so much social stigma attached to it and the challenges of being alone with a SEN child.

## National Health Commissioning Board

Ensure NHS providers, Foundation Trusts and other providers in charitable and non profit sectors understand the financial reasons for providing prevention services and the need for paediatric and adult complex care provision.

### CCGs

- Create necessary policy and provision within their locality.

CCGs could have a policy regarding the availability of IVF treatment and Sterilisation. IVF clinics need to be able to refuse women taking teratogens. Women who take teratogens need to be offered sterilisation if that is what they want. I was fortunate to be sterilised over 10 years ago, others are not so lucky and rely on the oral contraceptive which isn't always effective with Valproate, this leads to unplanned pregnancies and more cases of Valproate Syndrome.

Geneticists need to have the clearance from the NHS Trusts executive to diagnose valproate syndrome. I feel there may be some reluctance due to the investments the pharmaceutical industry make in hospitals and the potential for lobbying to lower the number of reported cases. My Son cannot pursue any further legal action against Sanofi due to the conditions of the discontinuance notice signed when funding was withdrawn from the FAC Litigation. Other children may be able to

pursue Sanofi in Court. Diagnosis would enable them to pursue Justice. Health grants and compensation schemes will be investigated by campaigners. Diagnosis will also be necessary for the child/adult with Valproate syndrome to be included in any settlements.

## Health Education England

Ensure Education and Training Board are delivering information.

## Department for Education

The Department for Education also has a role to play. Elizabeth Truss confirmed to my MP on my behalf that Teratogens are taught in KS3 and KS4 in Science and PSHE. Teachers have to find their own resources as there is no government information available.

PSHE is a non statutory part of the National Curriculum so the discussion surrounding family planning and preparing for parenting will often not be taught in Faith schools, Free schools and Academies. Faith is a major reason why contraception is not used and to deny these children the opportunity to shape their futures could be seen as morally irresponsible.

Science could effectively teach about teratogens but I don't think there would be the time to discuss the implications to individuals of taking teratogens while pregnant the lifelong effect this will have on the entire family. I'm not familiar with the Science National Curriculum but would assume that lessons would focus on Human Biology and the reproductive system.

Teacher resources I have found mainly discuss illegal drugs, tobacco and alcohol. I don't think it suitable to have private conversations with girls on medication as it will only increase the feeling of 'I'm different' and add to the lack of confidence many children with health conditions experience.

Teaching of teratogens should be compulsory. Informed choice is essential. Resources for teachers need to be endorsed by Dept for Education and Dept of Health.

## 7. 'Dear Lawyer' letter and further documents

[Type here]

Dear.....,

I have found your details on Legal 500 and Chambers & Partners website in relation to your expertise representing Claimants in the field of Product Liability, Human Rights and Personal Injury.

My Son was a test case in the FAC Litigation that had it's Legal Aid withdrawn in 2010 due to Legal Services commission funding review assessing the case as having a poor probability of success.

An application of Legal Aid for a Judicial review into the LSC decision was also denied and the Lord Chancellor refused to act and investigate the Public Interest element as he said it was an LSC decision independent of government intervention.

The European Medicine Agency PRAC review in 2014 accepted the 30-40% risk of neurodevelopmental delay and updated warnings and prescribing guidance in all member states for all Valproate products.

In the UK this has led to the MHRA Valproate Toolkit being created by the Valproate Stakeholder Network and disseminated using the central alerting system, drug safety update, Dear Doctor letters to all CEOs of NHS Trusts and CCGs, updates to GP prescribing software, cards sent to pharmacists to be given to females with Valproate prescriptions and a warning on the outside of the Valproate box.

Cases have been settled in the USA regarding Depakote, and in France an independent report commissioned by government resulted in the French Government agreeing to compensate French Depakine victims and enabling legal action against Sanofi by a group of Claimants.

UK prescribing data and the 40% risk of defect with Valproate has estimated 20,000 people in the UK have been affected over the last 40 years.

It was noted in Committee on Safety of Medicines minutes and correspondence in the 1970s that Valproate teratogenicity should be monitored due to evidence of physical malformations but that patients should not be informed to avoid panic.

Prescribing guidance changed in the 1980s and files of the minutes from the Committee of Safety of Medicines in the 1980s are sealed for 100 years citing patient confidentiality as the reason.

20,000 people in the UK have Valproate syndrome though most are not diagnosed.

Children, in effect, were denied Access to Justice when Legal Aid was withdrawn as they didn't have the financial means to continue.

Discontinuance notices were signed by the majority of Litigation friends to protect them against responsibility for Sanofi costs. In signing this discontinuance, Claimants would not be able to pursue Sanofi or a Third Party for their damages in the future.

Letters to Government Ministers have shown a refusal by Government to compensate victims or grant financial support for Legal aid.

However, my most recent response from the Department for Justice has not said 'no' and has suggested approaching the Legal Aid Agency for Exceptional Case funding.

I am awaiting responses from the Department for Education, Department of Health and Department of Communities and Local Government regarding ringfenced funding for the services required for people with Valproate syndrome.

Their syndrome is not understood so many have received inappropriate medical treatment, educational provision and social care.

The services they do use are being cut or relocated and they are increasingly becoming isolated and vulnerable with no financial security along with their family carers.

I consider there to be four areas for potential group Litigation.

- Product Liability
- Human Rights
- Personal Injury
- Scientific, governmental, regulatory complicity

Would you be interested in representing a group of children and adults in any of the above areas to ensure they can get Justice and recompense for the injuries incurred?

Would you be interested in representing NHS Trusts and Local Government to pursue Central Government for additional ring fenced funding for provision required by people with Valproate Syndrome?

Would you be interested in representing us to get a Judge led Public Inquiry into why Valproate and other pharmaceutical teratogens have continued to be unmonitored and prescribed without warnings and victims been left unable to Access Justice?

Additional information attached.

Many thanks

Emma Friedmann

Mother of Adult with Valproate syndrome.

FACSAware Campaign Director

Member of MHRA Valproate Stakeholder Network

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### Letter from Lord Chancellor

8th November, 2010

Dear Mrs.xxxx,

Thank you very much for approaching me and my office about the decision to withdraw legal aid from the claim against Sanofi-Aventis and the dreadful problems which may have been caused by their drug Epalin. As I think my PA explained to you, decisions on legal aid are made by the Legal Services Commission, which is an entirely independent body. Ministers do not take any part in individual awards of legal aid and the Commission has to be free of political influence in taking decisions in individual cases. I think that Members of Parliament who lobby them will be told that

they cannot respond to political lobbying. I actually think that it would be quite wrong for the question of funding of individual legal actions to be the subject of political debate or campaigning.

My understanding is that the Commission took their decision because they received legal advice that the claim was unlikely to succeed. This is not a new rule

in our legal aid system and it has applied ever since

the system started. The tax payer can only finance claims where expert legal opinion advises that there is some reasonable prospect of success. The result is that an adverse opinion from senior lawyers will almost always mean that the legal aid is withdrawn.

I realise that this is desperately disappointing for the people bringing the claim. I have no doubt that the women involved have had an appalling experience and will never be able to completely get over it. Independent lawyers and experts have, however, decided that further litigation would be likely to be fruitless and there really is no way that anybody can avoid taking a decision in the light of that advice.

Yours sincerely,

From Ken Clarke

[National Archive Files](#)

REFERENCE NUMBER	TITLE	YEAR	NOTES	
BS 6/288	DM (78)22	Extracts from Meds & Money	24/02/1978	
BS 6/1513	E/1517	Ass of clinical prof of medicine	1976-79	
BS /6/2848	DM (78)15	DHSS Press, medicines advertising & labelling	01/02/1978	
MH 171/31	CSD/S/165/42	Comparison in incidence of reaction reports	01/01/64 – 31/12/71	Com on ARs & med res council
MH 171/41		Warning, Dangers of new listed drugs, product license regulations		Committee of Safety of Drugs
MH 171/56		Status reports	1964-1971	CSD
MH 171/57		Correspondence	1962-1967	CSD
MH 171/58		Correspondence	1967-1969	CSD
MH 171/64	CSM/AR/58v1	Drugs and congenital abnormalities	1964-1969	Committee of Safety of Meds
MH 171/62		Reporting of AR by pharma	1963-1971	Ass of Medical Advisors
MH149/1922		Action on marketed meds	1967-1972	Dunlop Com on safety of drugs
MH 171/64			1964-1969	
MH 171/65		Congenital Abnormalities	1970-1971	
MH171/21		Notifications to committee of Adverse Reactions	1970	Committee of AR
MH149/1047		Working papers & draft report	1971	CSM
MH171/26		Letter to Doctors. New form for notifying ARs	1963-1966	
MH171/27		Yellow Card	1964-1971	
MH148/569		Minutes, Agenda, Papers	1975-1976	
MH148/563			1968-1969	
MH148/564			1970	
MH148/567			1972-1973	
MH148/568			1973-1974	
MH171/61		Committee on Adverse Reactions	1974	Prof L J Witts
MH154/1215		Vaccinations	1978-1983	

REFERENCE NUMBER	TITLE	YEAR	RELEASE DATE	
MH154/408/1		Measles Vaccination, 10 pages	1970-1976	2071
MH154/631/1		Vaccination, 27 pages	1967-1981	2061
BN116/257	ARVI/84/3	Agenda minutes papers: CSM & Com Vaccine Immunisation	05/10/84	01/01/2085
BN116/255	ARVI/84/1	Agenda, minutes, papers	03/02/84	01/01/2085
BN116/254	ARVI/83/3	Agenda, minutes, papers	28/10/83	01/01/2084
BN116/253	ARVI/83/2	Meeting 2	01/07/83	01/01/2084
BN116/352	ARVI/85/2	Meeting 2 Agenda	07/06/85	01/01/2086
BN116/353	ARVI/85/3	Meeting 3	04/10/85	01/01/2086
BN116/256	ARVI/84/2	Meeting 2	01/06/84	01/01/2085
BN116/351	ARVI/85/1	Meeting 1	01/02/85	01/01/2086
BN116/252	ARVI/83/1	Meeting 1, Agenda missing	04/03/83	01/01/2084

## Estimates of number of people in UK affected by Valproate by Dr Rebecca Bromley

The Review does not currently have permission to publish this section, however this document can be found on the FACSaware Facebook group. In addition, Dr Bromley, Professor Clayton-Smith, Professor Turnpenny and Professor Wood have provided information in their submission, please see [Clinicians, academics and other individuals – Sodium Valproate](#).

## Education provision letter by Dr R Bromley & Prof J Clayton Smith

Dear Parent or Teacher,

We have been asked by OACS to provide some information for parents of children who have been diagnosed as having a fetal anticonvulsant syndrome or whose children were exposed in the womb to antiepileptic medications and who are now having difficulties.

Fetal Anticonvulsant Syndrome is the name given to a distinctive pattern of physical features, birth defects, learning and neuropsychological problems detected in a child whose mother needed to take certain medications during pregnancy.

There are currently only 3 confirmed Fetal Anticonvulsant Syndromes and these are named after the medications that the syndrome is associated with:

- 1) Fetal Valproate Syndrome
- 2) Fetal Carbamazepine Syndrome
- 3) Fetal Hydantoin Syndrome

Children who have a diagnosis of one of these syndromes will have been reviewed and diagnosed by a Clinical Geneticist or a Specialist Paediatrician. To make a diagnosis the Doctor will review the child for a constellation of physical and development features consistent with the syndrome. This diagnosis cannot be confirmed on a blood test and is based on the pattern of problems with which the child presents. In many cases, however, the doctor may have tested to rule out other common causes of learning problems. Research and experience suggests that Fetal Valproate Syndrome is the most common of the Fetal Anticonvulsant Syndromes.

### Learning and Development

Whilst our knowledge about the development of children exposed in the womb to antiepileptic drugs is improving we still do not have a comprehensive understanding of the development of cognitive abilities over the later childhood and adolescent years. What is provided here is a summary based on research completed to date and on clinical experience.

Published research demonstrates that children who have been exposed to sodium valproate (trade name Epilim in the UK) in utero are at an increased risk of having difficulties in one or more areas of cognitive functioning. The most common difficulties are:

- Language difficulties (expressive and comprehension)
- Attention difficulties
- Working memory difficulties
- Memory for verbal information (things told)
- Poorer levels of intellectual ability (likely due to other cognitive difficulties)

- Difficulty writing for long periods due to joint laxity
- Social difficulties

Children with Fetal Anticonvulsant Syndrome may also have a number of physical problems which might affect them at school. These include:

- Lax joints leading to clumsiness, difficulty in walking long distances and difficulty in writing
- More difficulty with toilet training and bladder control
- Tendency for ear infections in childhood which can lead to time off school and hearing problems
- Long or short sight. Vision should be checked if there are any concerns.

As with all children, each child with fetal valproate syndrome (FVS) is unique and may not display weaknesses in all of the above areas, however most children will show a degree of deficit within their language processing abilities. Difficulties in these cognitive areas may in turn impact on other areas of cognitive ability such as intellectual functioning, memory ability and social functioning.

Recent research has also shown that children exposed to sodium valproate in the womb are at an increased risk of being diagnosed with an autistic spectrum disorder. Whilst this risk is larger than in the general population, it is still relatively small at 4-8% of children exposed to sodium valproate. It is thought that children are more likely to receive this diagnosis because of the language and social difficulties they experience.

On the whole, fewer children appear to be affected by exposure in the womb to phenytoin (Trade name Epanutin in the UK) or carbamazepine (trade name Tegretol in the UK). However a number of children do experience difficulties in their cognitive abilities following exposure in the womb to these medications and a small number will be diagnosed as having a fetal anticonvulsant syndrome or fetal carbamazepine syndrome. Less is known about the abilities and impairments of children with a history of phenytoin or carbamazepine exposure but from the limited information we have it appears that they are more likely to struggle with language development and verbal tasks and are possibly more likely to have poorer concentration skills.

Cognitive difficulties such as these present a huge challenge to the child, to their parents and to their educators. Children with a fetal anticonvulsant syndrome or those with cognitive difficulties following exposure to an antiepileptic medication do not always meet the criteria for special school or learning disability support. This can understandably lead to frustration for parents who want to see their child supported in the best way possible.

Advice on how to help your child

A good working relationship between school and home is key.

It is important that everyone has a full understanding of your child's cognitive abilities and that their personal strengths and weaker areas are documented. Information on cognitive strengths and weaker areas is key to assisting education and providing learning support at home.

A comprehensive neuropsychological assessment should be carried out by an Educational or Clinical Psychologist to give a full understanding of how your child's brain is functioning. Sadly this is easier said than done due to Educational Psychologist budgets being incredibly tight and the services offered by Clinical Psychologists varying from area to area. As a first step speak to your child's teacher and the special educational needs officer (SENCO) at the school. Enquire as to whether the school is in a position to fund Educational Psychologist time for a formal neuropsychological

assessment. If the school is unable to assist with this it will be worth contacting your local Child Development Centre or Child and Adolescent Mental Health Service (CAMHS) for advice on a referral to them for a formal neuropsychological assessment. It is worth bearing in mind that you will need to be referred in to NHS services by your GP or Paediatrician and that waiting lists can be long due to high demand for services.

It is important that the neuropsychological assessment includes an assessment of language (expressive and receptive), attentional capacity, rate of learning and of general memory functioning as well as intellectual functioning. Some children with a fetal anticonvulsant syndrome may have an intellectual ability within the low average range but may have language and attentional deficits which are much more severe. The abilities of children change over time and an assessment completed three years or more ago may not be a reliable reflection of your child's abilities now.

Where possible an Educational Psychologist or SENCO could be consulted in the planning of lessons for your child. Each child is an individual but generally, due to the severe impairment in attentional and working memory abilities, children with a fetal anticonvulsant syndrome are likely to struggle in the classroom to follow instructions and to retain information, especially if the information is presented verbally.

It is really important to have a good working relationship with your child's school. Strategies to maximise your child's learning within the class room will also be useful to employ at home. As parents you are in a unique position to support your child and complement the work completed at school. Daily tasks to revisit information covered at school during that day may prove to be useful. Small rewards can be useful to keep a child motivated and should be used to praise effort and not necessarily achievement.

The language difficulties experienced by children with FVS may also lead to social difficulties within their peer group. Talking through difficult social situations with your child (e.g. an argument with a close friend) explaining the reasons and the consequences involved will enhance their understanding of social interactions and the intentions of others. Formal social skills training or social inclusion packages designed for children with other difficulties (such as Autistic Spectrum Disorder) are likely to be useful but their availability depends very much on the facilities of the individual school or local NHS child services.

Our knowledge of children with FVS is increasing all the time and we will update this advice letter as it becomes available.

Yours sincerely,

**Dr Rebecca Bromley**  
**Clinical Psychologist**  
**Royal Manchester Children's Hospital**

**Prof Jill Clayton Smith**  
**Consultant Clinical Geneticist**  
**St Mary's Hospital, Manchester**

#### [Question for Secretary of State for Justice.](#)

2nd January 2017

It has become increasingly clear that Epilim has caused physical and neurodevelopmental birth defects and this is now accepted by Sanofi. Children were in effect denied Access to Justice when Legal Aid was withdrawn from the FAC Litigation in 2010. Since 2012 parents have lobbied the MHRA to get warnings issued. The Valproate toolkit was developed in 2015 and disseminated by the MHRA

in 2016. Parents continue to work with the MHRA.

Justice and the Rule of Law is an essential part of UK Democracy:

- What plan does the Government have to ensure these children (now adults) can access Justice?
- Will the Government grant funding to enable the reopening of the FAC Litigation?
- What additional financial provision is being made available to Local Authorities to ensure they can continue to provide essential specialist education and child and adult social care support to families affected?
- Will the Government consider pursuing Sanofi for the avoidable financial cost to public services their product Epilim has caused?

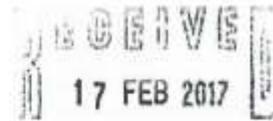
Many thanks  
Emma Friedmann  
Leicester

**Response from Justice Minister**

The Right Honourable  
Sir Oliver  
Heald QC  
MP

Ministry Minister of State for Justice of Justice

Jonathan Ashworth MP House of Commons  
London  
SWIA OAA



MP ref: JA/DK/01170020  
MoJ ref: MC040364

A handwritten signature in blue ink, appearing to read "Jonathan Ashworth". The signature is fluid and cursive.

7

February 2017

#### UK EPILIM VICTIMS

Thank you for your letter of 5 January, addressed to the Lord Chancellor, regarding legal aid for those affected by the epilepsy drug Epilim. I am responding to the concerns you have raised which fall under my area of Ministerial responsibility.

In your letter, you enquire about legal aid funding for Fetal Anti Convulsant Litigation. The availability of funding will primarily depend on whether any further litigation takes place, and whether an application for funding is submitted. Any such application would be for the Director of Legal Aid Casework to consider. The Director would need to be satisfied that, in the specific circumstances set out in any application, the civil legal services sought were in the scope of legal aid and that the relevant means and merits criteria were met so that litigation funding may be made available.

Where a matter might fall outside of the scope of the legal aid scheme, consideration could also be given to whether an application for Exceptional Case Funding (ECF) would be appropriate. The ECF scheme ensures that funding will continue to be provided (subject to means and merits) where:

- (i) failure to provide legal aid would breach the applicant's rights under the ECHR or
- (ii) EU law; or in the light of the risk of a breach, it is appropriate to provide legal aid.

Again, whether the case meets the relevant requirements for ECF would be a matter for the Director of Legal Aid Casework, whose decisions in individual cases are wholly independent of Ministers.

You also reference Local Authorities and financial provision for specialist education advice as well as the question of the government pursuing Sanofi for the financial cost to public services, as a result of their product. These points extend beyond this Department's area of responsibility and so I have sent your correspondence on to the Department for Communities and Local Government, the Department for Education and the Department of Health, who I trust will be able to address your concerns in full.

A handwritten signature in blue ink, appearing to read "Sir Oliver Heald". The signature is fluid and cursive.

SIR OLIVER HEALD QC MP

## EU and UK Constitutional Law

Inadequacies of the Consumer Protection Act regarding pharmaceutical harm was raised in the the Debendox debate in 1984. The decision was that it wasn't an appropriate time to change it as UK was joining EU Laws.

Post Brexit the EU Product Liability Directive will no longer be used so a robust Consumer Protection Act needs to be in place that reviews terms of reference relating to product, payment, defect and recompense.

Medicine regulation is being changed globally, in the USA the 21st Century Cures Act 2016 will lower regulatory standards as less evidence will be required prior to approval by the FDA. The UK will no longer be part of the European Medicines Agency. The MHRA has inadequate funding to do the work currently done by the EMA. The UK Deregulation Bill aims to lower the regulatory bar.

Fast tracking of medicines and devices will undoubtedly save some lives but the risk of Adverse Drug Reactions will also increase.

Victims of pharmaceutical harm need to be covered as the current and proposed systems are not economically viable for victims or the State.

### Online links

#### French IGAS report

[www.igas.gouv.fr/IMG/pdf?2015-094R.pdf](http://www.igas.gouv.fr/IMG/pdf?2015-094R.pdf)

#### Debendox Debate

<http://hansard.millbanksystems.com/commons/1984/jul/25/debendox>

#### Valproate toolkit

[www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients](http://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients)

#### Sodium Valproate – The cost

<https://youtu.be/Mi89I7qkCJ8>

#### Guardian – Jon Robins

[www.theguardian.com/law/2011/feb/01/epilim-compensation-case-roll-call](http://www.theguardian.com/law/2011/feb/01/epilim-compensation-case-roll-call)

#### BBC Radio 4 - File on 4 – Bitter Medicine

<http://www.bbc.co.uk/programmes/b00xhh70>

## 8. Response to 'Dear Lawyer' letter

The Review does not have permission to publish this at this point. However this, and other documents provided by FACSaware, are available on the FACSaware Facebook group.

## 9. Executive Summary

### Executive Summary

- It has been proven beyond doubt and accepted by the pharmaceutical industry that there is an increased prevalence of physical and neurodevelopmental birth defects when Valproate is taken during pregnancy.
- Those exposed have lifelong disabilities and have been unable to access justice in the UK courts.
- The services required by those affected and their families are highly specialised.
- The taxpayer is paying for the services required and the pharmaceutical industry is not contributing.
- Our regulatory system is broken and needs to be fixed.

### Our Wish List.

- Immediate additional funding for local education, health and care services.
- Immediate and lifelong financial security for those exposed to Valproate who present symptoms of Valproate Syndrome.
- Appropriate services delivered and co-ordinated by professionals who have an understanding of Valproate Syndrome.
- A Judge led Public Inquiry into medicine and devices regulation to focus on Valproate.

The full report will be published on FACSaware facebook page at 6pm on 7th December 2017.

The full report contains testimony of those affected, a thorough breakdown of the Wish List and requirements of a Public Inquiry.

If you would like an electronic copy of the report please contact [REDACTED]

## 10. Valproate – Report for APPG 4<sup>th</sup> December 2017

#FACSaware  
Valproate

Prevent Suffering, Improve Lives

Report for Norman Lamb MP and AED in Pregnancy APPG Compiled &  
written by Emma Friedmann and David Body  
4th December 2017

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## Executive Summary

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- Appropriate services delivered and co-ordinated by professionals who have an understanding of Valproate Syndrome.
- A Judge led Public Inquiry into medicine and devices regulation to focus on Valproate.

## Contributors

Members of FACSaware facebook page.

Individuals with Valproate Syndrome.

Parents of children and adults with Valproate Syndrome.

Foster parents of children with Valproate Syndrome.

Other Pharma Harm campaigns.

Interested medical and legal professionals.

Attendees of European Medicines Agency Valproate reviews.

Attendees of MHRA Valproate Stakeholders Network.

Facebook  
Twitter  
Youtube

## Foreword

### Prevent Suffering, Improve Lives

FACSAware is an online awareness campaign set up by the Fetal Anti Convulsant Trust. Reports written for media, regulators and politicians are based on views expressed through our networks. These reports are shared publicly on the FACSAware facebook page.

We are not a registered charity and have no board or bank account.

We do not claim to provide medical advice but by sharing our experiences we inform and support each other and signpost to services that may be useful or of interest.

We do not have formal membership or claim to represent all those affected.

From 2012 parents have lobbied the MHRA, RCGP & BMA to issue a 'Caution in Use' drug safety update for Valproate in pregnancy. #FACSAware was launched in 2013 with a demonstration outside the MHRA offices. Valproate was referred to the EMA PRAC in October 2013 and warnings were issued by the MHRA in the UK in November 2013.

Some of our campaigners attended a meeting at the Department of Health in 2013 with Norman Lamb MP in his role of Social Care Minister to discuss Valproate. Since then we have worked with Alec Shelbrooke MP to address issues related to Valproate at his Thalidomide APPG in 2014.

From 2014 we have been involved in the EMA PRAC and the MHRA Valproate Stakeholders Network to establish what is needed and to develop resources to enable women to make an informed choice about anticonvulsants and to reduce the number of children born with avoidable disability.

Search #FACSAware for media interviews.

Many of us have had communications with our constituency MPs, we have focussed on raising awareness through the regulatory frameworks. We have had success in persuading the MHRA about the strength of evidence showing causation of injury by Valproate. As a result, warnings of risk in drug packs and in the British National Formulary are more specific and reflect the international research consensus. Women affected by epilepsy should now be in a position to make an informed choice with their clinicians about anticonvulsant and mental health treatment. Now that is in place we are better placed to lobby politicians to recognise the personal and economic impact to those affected by Valproate.

I hope you will take into consideration our views when deciding on an appropriate course of action.

Many thanks for your interest.

Emma Friedmann

# Wish List

These items reflect the needs of Valproate affected children/adults

## 1 Ring-fenced funding

### **Immediate and ring-fenced funding for local services people with Valproate syndrome and their families need.**

Cuts to local government and NHS budgets have left many families with inadequate services. Voluntary sector organisations who historically provided advocacy, respite and recreational activities are finding the economic environment challenging as grants they relied upon are no longer available.

Jon Ashworth MP is awaiting responses from the Department for Education, Department of Health and Department for Communities and Local Government regarding ring-fenced funding to secure these vital services.

The Ministry of Justice forwarded the correspondence to the above departments in the Spring 2017 and Jon Ashworth MP (on behalf of his constituent) has chased this up since the General Election but has still not received a response.

The new structures, short staffing and fragmentation of the NHS is affecting the quality of care those affected need.

*“My daughter’s adult social care is under-funded and therefore she is not supported sufficiently”  
“My son is in independent living accommodation, the carers are not good, always bringing in agency and bank staff”*

*“I’ve waited 3 months to be allocated a social worker”*

*“Policy appears to be that key workers are changed regularly so that service users don’t get too attached”*

*“We’ve struggled to get Speech and Language therapy”*

## 2 The need more accurately to define those affected by Valproate

### **Individuals need support, appropriate services and welfare assessments.**

Evidence based research has shown a 30-40% risk of neurodevelopmental and physical birth defects.

Prescribing data shows how many women have been prescribed Valproate.

The lowest estimate of the number of children affected over the last 40 years is 7,000.

The highest estimate is 20,000 affected.

As successive governments are partly to blame for Valproate warnings not being issued sooner and

Access to Justice being denied we see it as the government's responsibility to provide all necessary services to those affected and their families.

Those affected need to be found so they can be given the support they need.

*"There needs to be a NICE guideline so that from primary care level, GPs recognise these children early and families are supported accordingly"*

*"How do I get a diagnosis for my children?"*

*"I have Valproate syndrome. My brain is like a puzzle missing when I am really confused and I get annoyed", "my weakest is standing up for myself, I find it hard to talk to someone, the hardest is talking to my teacher"*

*"I am feeling terribly guilty, angry and upset. I have no support from my doctors because they do not understand"*

*"I had to have mental health medication to manage the stress of looking after my son's challenging behaviour"*

### 3 A lump sum payment

#### **Many families with disabled children/adults face financial hardship.**

Parents have had to give up work due to care commitments, families have had their homes reposessed, children and adults have not had an accurate diagnosis and are therefore excluded from many state benefits.

We need habitable housing and the opportunity for long term ownership or tenancy to provide stability to the adults and children affected and access to local support services.

Adult social care is a postcode lottery. Adults with Valproate syndrome need to be safeguarded.

They need good quality accommodation, experienced support staff, the opportunity to access educational and recreational activities in a safe environment.

The stress parent carers and siblings experience is vast. Our children have challenging behaviours and are excluded from many social activities. Reliable, safe respite is not available to most and if parents choose a private provider the cost is huge and many of the staff are not experienced in complex disabilities and are on temporary contracts.

Those affected need to be able to fund suitably adapted housing and to be able to fund ongoing upkeep.

### 4 Annual Health Grant

#### **A regular payment for life for those affected to be administered by professionals.**

Many of our children cannot make informed decisions and need someone to manage their finances, health benefits and social care entitlements.

Parent carers will not be there to look after their children for life as they are likely to die before their children.

There needs to be an annual index linked payment to meet the needs of those unable to work because of Valproate injury, over and above basic benefits entitlement.

*“It is so important that our children get access to funds and appropriate support for the rest of their lives, we are not going to be around forever to fight for their needs and support them”*

*“What happens with inheritance? Will benefits be taken and no care provided until the money has run out?”*

*“She needs to be taken care of financially by people who wouldn’t take advantage of her money but would help her deal with it responsibly”*

*“He needs life-long care that maintains his mental and physical wellbeing and provides for his material needs and moderate wants”*

## 5 Educational provision

### **Many children and young adults with Valproate syndrome are not receiving appropriate education.**

Either there is no local provision with experience and resources to manage their needs or the transport to and from school is not safe or accessible.

Parents try and get an Education, Health and Care Plan but are denied by professionals who do not understand the child’s needs. Parents have had to pursue tribunals to get an EHC plan and when they finally succeed in getting one, the educational, health and care provision made available falls short of what is specified as needed.

*“There were often lads in groups calling out and laughing at him”*

*“My daughter has highly sensitive hearing and I can’t find a school that can provide for her”*

*“Many of us need help and counselling to understand this. How will I tell my children?”*

*“There isn’t a suitable specialist school in my area, I have to keep my daughter at home. I have no help with home educating and physiotherapy has been suspended because she is no longer in school”*

## 6 Education for professionals

### **Professionals have no understanding of Valproate syndrome.**

Parents who suspect their child has been affected by Valproate approach their GPs and Special

needs co-ordinator in school. These professionals have no knowledge of Valproate syndrome and do not connect the complex symptoms that present.

Young adults have had to attend DWP Work Capability Assessments and the assessors do not have an understanding of their needs. Personal Independence payments and mobility vehicles have been withdrawn.

NICE need to issue guidelines on the diagnosis pathway for Valproate syndrome and other teratogen related conditions.

NICE need to issue information on how the syndrome presents with a link to the treatment pathway for each symptom.

*"A specialist to screen the children/adults for any likely hidden health problems and to act as care pathway co-ordinator to ensure all health and social care needs are met"*

*"Training and recognition to both education and health professionals on what types and problems children and adults with Valproate syndrome face"*

*"I'm still trying to educate the powers about our son after almost 30 years"*

*"The main problem though out my daughter's life has been inadequate understanding of her needs and therefore not receiving the correct support to help her reach her potential at each stage of her life"*

*"My daughter's adult social care is under-funded and therefore she is not supported sufficiently"*

*"In my experience, relatives don't even understand so he is left alienated by others. What are his chances for the future?"*

*"I've got family but they really don't understand her needs. Who is going to look after her?"*

*"I am feeling terribly guilty, angry and upset. I have no support from my doctors because they do not understand"*

## 7 Judge led Public Inquiry

### **Action and inaction has led to this tragedy. Who is responsible for what?**

Victims were denied access to justice due to lack of financial means when legal aid was withdrawn from FAC Litigation in 2010.

The Ministry of Justice suggest we apply to the Legal Aid Agency for exceptional case funding, but we cannot find a Law firm who are willing to represent those affected.

Those affected by Valproate need to have access to justice and appropriate recompense.

*"I would like all discussions regarding our children's futures to be completely transparent and open, not governed by any one organisation"*

*“My Son was denied Justice when Legal Aid was withdrawn in 2010, we had to sign discontinuance notices and agree never to pursue legal action again, what is going to happen to him”*

*“Those responsible accept responsibility”*

*“Compensation for the avoidable effects”*

*“It is imperative that my son must be recompensed for what he has gone without”*

## **Valproate is not the only medical or pharmaceutical product to cause lifelong harm to patients.**

Valproate is a good example of a drug licensed over a very long period of time which has been recognised to cause a series of lifelong injuries. Specifically to the children of some of those using the drug to avoid seizures during pregnancy, but it is not the only medical product that has been licensed to do good which has caused harm.

UK medicine regulators have often been slow to react when such harms occur, and a need arises either to withdraw a product or modify it to enhance patient safety. There is a belief that our current system is not adequately safeguarding citizens and putting patient safety first.

Any Inquiry needs to examine medicine and devices regulation and licensing taking into consideration other products that have caused harm or been suspected of causing harm. The form that that Inquiry should take is set out below

### **Taking Valproate as an example., concerns are that;**

Dissemination of Valproate warnings using current UK systems has been inadequate as highlighted by the European Medicines Agency and the MHRA in 2017.

How can a drug as toxic as Valproate continue to be prescribed without warnings?

What was known, by who and when?

Was information withheld?

Who made decisions?

What evidence was used to inform their decisions?

How can the regulatory system be improved?

How can we make sure this never happens again?

Why are those affected by adverse drug and device reactions denied legal aid funding?

*“Many people have been party to not mentioning the negative possibilities”*

*“We need to know how this happened and why, so we can avoid similar situations in the future”*

# The form of a suitable Public Inquiry

## Why do we need a Public Inquiry?

**A Public Inquiry into medicines, medical devices and medical products licensing and regulation is required because:**

**The UK will no longer be part of the European Medicines Agency post Brexit.**

The MHRA is not equipped or structured to manage the additional workload and ensure Patient Safety.

**Many people have preventable disabilities caused by medical product side effects.**

Everything we consume has risk. What risk are we prepared to accept? How can we make medicines and medical products safer?

**Victims and their family become reliant on public services paid for by the taxpayer – rather than the Manufacturer which caused the harm. The economic impact of injuries inflicted upon a group of up to 20,000 people is huge.**

Many will never work and they rely on already stretched public services, they have less spending power and there is a loss in tax revenue from those affected and their family carers who cannot hold full time jobs.

**Innovative medicines need to be fast tracked.**

The current regulatory system is not equipped to ensure the safety of new medicines and the recording of efficacy and risk. Commercial sensitivity is used as an excuse to withhold data. Medical Product regulation needs to be structured in a way that moves away from initial licensing followed up by half hearted follow up and moves towards a system of initial precautionary licensing followed by a rolling review and post marketing surveillance in which patient safety is the paramount consideration.

## What does a Public Inquiry need to include?

**Judge led.**

Medicine regulation files are held in National Archive and some seem to have been sealed for 100 years. Other confidential files exist.

A High Court Judge needs to head the Inquiry and be empowered to demand disclosure of documents and summon witnesses to attend. 'Commercial confidentiality' should not be a basis on which documents are withheld from the Inquiry

Evidence must be given under Oath.

**Witness evidence.**

Evidence should be required from Patient groups, MHRA, CPRD, Pharmaceutical industry, Product Liability and Personal Injury Lawyers. As well as Public service providers and the Legal Aid Agency.

Declarations of interest must be compulsory by all those involved to ensure pharmaceutical influence does not dominate the inquiry.

**Scope: Historic and current examples of adverse outcomes** which the Inquiry should review and upon which it should receive evidence:

Primodos, Debendox, Vioxx (all withdrawn from the market). Valproate, Seroxat (still prescribed). Metal on Metal Hip Replacements, PIP breast implants (withdrawn). Mesh. Contaminated blood products.

**What happened that was good?**

**What could have been done better?**

**Effectiveness of the Yellow Card ADR reporting system in spotting trends in Adverse Incidents.**

**Effectiveness of the CPRD digitised health records database.**

**Examination of the influence of pharmaceutical industry on policy and people - positives and negatives**

**Identifying the extent that the patients' interest was paramount in licensing and post market surveillance.**

Potential outcomes of such a Public Inquiry which could inform future Regulatory legislation

**Clarity in the language and format of risk/benefit.**

Patients and/or their carers need to be able to make informed decisions about treatment with their clinicians based on candid advice rooted in objective evidence.

**A no fault compensation Trust funded by the pharmaceutical industry to meet claims.**

Everything we consume has risk. A Compensation scheme needs to be set up and made available to those adversely affected by medicines and medical devices. The currently under performing Vaccine Damage Payment Scheme could be widened and equipped with suitable powers and independent status to fulfil this role.

**Regulator to give paramount weight to Patient Safety in setting standards for industry to abide by.**

Obliging manufacturers to produce objective evidence from post marketing surveillance and to report trends in both the nature and incidence of Adverse Events is of central importance. The MHRA need to be able to suspend licenses and impose fines if pharma and device manufacturers don't provide surveillance reports on their products and fulfil their reporting obligations on time and objectively.

**Teratogenicity risk to be an essential part of trials.**

All medicine to be used by females of child bearing potential needs to be assessed.

In order to maintain patient safety and develop scientific knowledge, babies exposed to teratogenic medicines in the womb should be monitored to adulthood.

**A safe system to fast track innovative medicines.**

Ensure new cures are found and research is collected on efficacy and the patient is kept informed of risk/benefit.

**Products with no extensive proof of risk/benefit should be 'Black boxed'.**

These products should be treated as experimental drugs and not prescribed without specific justification and accurate recording of desirable and undesirable effects.

**Fewer people harmed by medicines, devices and medical products.**

Patient safety needs to be the priority. Too many patients are avoidably harmed.

**Pharma encouraged to develop new products.**

Pharma need to have a framework to work within and need to know that if they fulfil their obligations their product will be fast tracked to market.

**Pharma to pay for the harm their products cause.**

If pharma have to contribute to a compensation scheme they will have an incentive to make safer medicines and the public purse will have more money to buy experimental drugs.

**All regulation to be carried out with patients' interest as the overriding consideration.**

## **Preparing for the future**

There needs to be a recognition that whilst medical and pharmaceutical products can have transformative effects, development of these products is not (and is far from being) an altruistic exercise.

These products need to be the subject of stringent regulation.

The danger is that post Brexit, with regulation in a single country rather than in an affiliation of 28 Member States, regulation of medical products will become what the manufacturers will be prepared to accept rather than what Patient Safety requires.

Prevent suffering, Improve lives

INFACT

Government Remit - Valproate

March 2018

Core Evidence



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## **INFACT Briefing Notes**

**(February 2018)**

- **Background to IN-FACT.**

The Independent Fetal Anti-Convulsant Trust (IN-FACT) was re- launched in November 2012 to support and giving relief and assistance to all affected persons whose disabilities were caused by their mothers taking a medication known as, or used as an Anti-Convulsant Medication to treat their condition during pregnancy. Not all children who are exposed to anticonvulsant drugs are affected and the level of risk is determined by known factors such as type of anticonvulsant and dose of anticonvulsant and unknown susceptibility factors. Children who are diagnosed with a Fetal Anticonvulsant Syndrome (FACS) are diagnosed by a medical specialist due to a constellation of physical and neurodevelopmental deficits they present with.

- **Prevalence of the problem.** It is estimated that around 0.5-1% of newborns may be exposed prenatally to an anticonvulsant drug. Sodium valproate reportedly carries the largest risk to developing infants and continues to be prescribed widely across a range of neurological and psychiatric conditions. According to prescription records (DINLINK data) there were over 21,500 women taking sodium valproate in 2010 in England and Wales. Scientific data demonstrates that around 10% of children exposed to sodium valproate will be born with a major congenital malformation (Samran et al 1997), their IQ is likely to be lower (Meador et al 2009), with 29% requiring additional educational support (Adab et al 2001) and with 6% being diagnosed with significant social-communication difficulties such as autism (Bromley et al 2008). With the latest research completed and published on 31<sup>st</sup> January 2013 (Bromley et al 2013) stating ' A 6 or 10 times increased prevalence of neurodevelopmental disorders is reported here for children with a history of prenatal VPA exposure respectively for monotherapy and polytherapy exposure....' 'The increase prevalence of ASD's within this group is consistent with [previous retrospective clinical research and reports from animal studies'

However, with the beginning of the work towards the release of the Valproate Toolkit on 8<sup>th</sup> February 2016, Minister for Life Sciences Mr George Freeman MP stated that there are 336 children exposed to Valproate every year, and figures from the Clinical Practice Research Datalink covering only 7-8% of the UK population, shows that 35,000 women aged between 14 – 45 years old are pregnant each year with only 30 receiving prescriptions for Valproate, therefore only 176 children are actually affected by the drug in pregnancy each year.

Even bearing this in mind, this still shows that approx. 7,000 children have been harmed by the drug Valproate since it first came onto the market in 1973, with a further 28 per month exposed to it.

- **History of the problem and the development of scientific knowledge over time.**

Throughout the 1960s, 1970s and 1980s a number of case reports were published in the medical and scientific literature which described children who had been exposed to one or more anticonvulsant drugs and had one or more major birth defects. These case reports described children who had been born with a range of defects including spina bifida, cleft palate, heart defects and limb malformations. Some of the children in these case reports were also reported to have mental retardation, neurodevelopmental delay or a learning disability whilst others were too young for this to be known. Birth defects occur for a number of reasons and individual case reports are not enough to show that the malformation in that child was likely to have been caused by the exposure in the womb to the anticonvulsant. A number of case reports however reporting the same type of defect in the children indicate that closer investigation is required, with the latest research in 2013 showing cause for concern due to the growing numbers of children with Neurodevelopmental problems and diagnosed Autistic Spectrum Disorders where the mother has taken Valproate during the pregnancy.

- **Group studies: Neurodevelopmental Outcome/Learning Disability**

Exposure in the womb to anticonvulsant drugs has also been associated with an increased risk to the developing brain which leads to what historically was termed 'mental retardation'. This term has been replaced with the term 'learning disability' in the UK and refers to someone who experiences difficulties in acquiring knowledge and skills to the level expected for their age. More recently research has turned its attention to the cognitive (thinking) and behavioural abilities of children exposed to anticonvulsants in the womb.

Similar to the findings relating to birth defects the type and dose of an anticonvulsant are important when assessing the level of risk to the developing child. There is less research into this risk but our current level of knowledge suggests that exposure to sodium valproate (Epilim) when the dose is above 1000mg daily carries the largest level of risk. Exposure at this level of sodium valproate (Epilim) has been reported to be associated with increased need for educational support and performance on IQ tests below the majority of their peers.

There is also evidence that children exposed to sodium valproate (Epilim) are at an increased risk of experiencing social-communication difficulties and are at an increased risk of being diagnosed with autistic spectrum disorders.

### **Sodium Valproate.**

The drug Sodium Valproate (Epilim) is manufactured by the pharmaceutical company Sanofi Aventis, amongst others, and has been prescribed in the UK since 1970s. Despite its efficaciousness for certain types of seizures, research has demonstrated that it carries a higher level of risk to the exposed foetus. The first case reporting the effects of Sodium Valproate during pregnancy appeared in 1981 and this grew to be a hot topic within the medical profession in the 1980's with numerous reports appearing in the Medical Journals. However, this was never investigated throughout the Review of Medicines between 1971 – 1990. The then Medicines Control Agency (MCA), which became the Medicines & Healthcare Regulatory Agency in 2004, did not pursue further the claims made by the medical research community. The MHRA Current Problems Reports touched on the effects of Sodium Valproate from the No9 issue in 1981 and continued to do so intermittently as did the Current Problems papers issued by the Committee on Safety for Medicines from 1983. Still no action was taken to convince the pharmaceutical company, then Sanofi Synthelabo, to re-call the drug or improve it, or to provide comprehensive warnings to patients.

From the early 90's the pharmaceutical company, which changed its name continuously during this time from Sanofi Pharma, Sanofi Winthrop and Sanofi Synthelabo becoming Sanofi Aventis in 2006, continuously insisted that the patient consulted the doctor for information when taking its drug during pregnancy, which is standard for a patient information leaflet. In 2005 Sanofi Aventis then added:

*'Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support'* with the addition of

*"Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal or have autistic disorders."* Following the collapse of the product liability litigation in 2011.

It is clear that both the Government and the pharmaceutical companies could have done more and taken further action to protect the public, with the belief it was the duty of Sanofi to keep up to date with known medical knowledge and to develop further research to ensure safety, passing this onto patients via the Patient Information Leaflet. It was the duty of Care of the MHRA to ensure Sanofi published warnings of the Teratogenic effects of its drug.

The delay in the establishment of research to investigate early scientific warnings and the failure to develop adequate preconceptional care for women requiring treatment with anticonvulsants during their child bearing years means that thousands of women have entered into pregnancy without being comprehensively informed about the level of risk, reducing their chances to make decisions about what treatment and at what dose.

Due to these delays it is our belief that thousands of children have been affected by exposure in the womb, and due to the lifelong nature of the deficits experienced by children and adults with Fetal Valproate Syndrome, that responsibility must be taken for these delays by the Government.

### **Committee on Safety of Medicines Knowledge**

Although all the above case studies and reports show that Anti-Convulsant drugs in pregnancy are harmful to the fetus, there has never been any confirmation or acknowledgment from Government to say that these drugs are, or are not safe to use until January 2013 when the MHRA issued notification to GP's and specialists following the European Review.

However, following INFACTs research on the topic of the earlier knowledge of Anti-Epilepsy Drugs (AED's) in pregnancy, we are now fully aware of the inside acknowledgment of the dangers of drugs such as Valproate, Phenytoin, Phenobarbital and Mysoline (now known as Primidone).

Since the late 1960's the Committee on the Safety of Medicine (CSM) were fully aware of the dangers of these drugs and it has been noted in minutes of meetings where the discussion of Cleft Palate etc.. due to AED's in pregnancy have been discussed.

In 1974 a report we completed on the new drug at that time which was Sodium Valproate (Epilim) and it was noted by the Pharmaceutical Company that this drug was Teratogenic in pregnancy. We are now aware that this information was kept away from the eyes of the patient and no such confirmation to anyone prescribed this drug was given until 2000 when the Patient Information Leaflet was changed by Sanofi to read:

***"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 in the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with Spina Bifida."***

We have however learned due to the European Review on Valproate in Pregnancy in 2014/15, that the MHRA, and the Medicines Control Agency before it have control over what Pharmaceutical companies publish on the Patient Information Leaflets and that this information was controlled by the MCA due to a statement made at a CSM meeting in July 1973.

Previous to this in June 1973 it had been noted that:

***"The Committee was informed that the Sub Committee in Adverse Reactions had accepted the Main Committee's view that it would be best not to mention the possibility of congenital abnormality following the use of anticonvulsants in relevant packaging inserts. The Sub Committee had still felt, however, there was a case for a mention to be made in data sheets to ensure that doctors were aware of the hazard, in part because of the possibility of litigation"***

The notes went onto state:

***"As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard, and that in the light of this the Sub-Committee would not consider it necessary to press for any further action"***

Instructions continued, and in July 1973 the CSM made another statement in the minutes of a meeting with the Sub-Committee for Adverse Reactions, it read:

***“The Committee was informed that the Main Committee had also welcomed the action by ICI Ltd [Mysoline] but had thought the evidence not sufficiently conclusive to require all other manufacturers of anticonvulsant products to use a similar statement, especially as it could give rise to fruitless anxiety. The Sub-Committee believed, however, that the character of the evidence was strong enough for an assurance to be given to the Main Committee on the account, but accepted the point regarding anxiety. Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that proposed by ICI could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients themselves seeing it”***

Following this in March 1974, on a Product Licence for Valproate it was stated:

***“for use in generalised, focal or other epilepsy. In women of child bearing age, it should only be used in severe cases or those resistant to other treatments”***

A statement also made in the Valproate Toolkit in February 2016.

Therefore, the subject was left in the doctors’ hands with them knowing about the damage Valproate caused but forbidden to tell their patients. This information was not repeated in the future years and so any new clinicians entering the profession following the 1973 letter would not have been alerted to the problem, the exact same instructions which took place in January 2015.

- **New Information from Government Bodies**

With the work of INFACT and meetings with the Medicines and Healthcare Products Regulatory Agency (MHRA) since August 2013, and following our input into the European Review into Valproate in Pregnancy, on the 8<sup>th</sup> February 2016 the Valproate Toolkit was released in the form of a Patient Booklet, Pharmacy Cards (on collection of a Valproate Prescription), Healthcare Professional Booklet and Checklist for Specialists.

However, following 2 surveys carried out by INFACT for both patients and pharmacists, we found that around 85% of patients were not receiving the Patient Booklet and around 90% were not receiving the Pharmacist card.

In a letter from Sanofi, on 27<sup>th</sup> May 2016 INFACT were informed that the Patient Booklets were not given to GPs as stated by former Minister for Life Sciences Mr George Freeman in a

Parliamentary Question in 5<sup>th</sup> May 2016, but they needed to be downloaded by GPs from the Sanofi website. The Parliamentary Questions stated that:

*“Letters and hardcopies of the toolkit were sent by marketing authorisation holders directly to General Practitioners (GPs)....”*

And we understand that even up to the 21<sup>st</sup> January 2017, patients were still not being recalled for their Epilepsy Review to have this information given or explained.

With the withdrawal of the Quality Outcomes Framework for Epilepsy in 2015 and the National Clinical Director for Neurology in April 2016, the system is certainly not addressing the issue of the dangers of Valproate and is not fit for purpose.

We therefore wish to suggest the following main points:

- Both the MHRA and the Department of Health were aware that Valproate was teratogenic and should have therefore collected data over the first 5 years of its arrival to the UK market as to its effects in pregnancy. The importance of early intervention should have certainly been the issue.

- NICE put guidelines in place ascertaining to the complications of Valproate in pregnancy in 2004 and stated

**13.2** *What information and counselling should be given and when?*

**199:** *In 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]*

In an e mail to IN-FACT dated 26<sup>th</sup> Sept 2012 NICE stated that:

*‘Once NICE guidance is published, health professionals are expected to take it fully into account when exercising their clinical judgment. Our guidance is evidence based and well respected. However, I can confirm that NICE has no role in monitoring the uptake of our guidance.’*

- Given that both the MHRA and the Dept. of Health were aware of the teratogenic risks of Valproate, why was there no guidelines or warnings in place before 2004 when the drug had been on the market in the UK since 1973.
- The Quality Outcomes Framework (QOF), in place to ensure information and guidance is passed to the public concerning medications and conditions, and also to ensure the NICE guidelines are followed was withdrawn from the equation for Epilepsy in 2015 and so there was no incentive for doctors to pass on the vital information concerning Valproate.
- Ever since 1973 there has been a system failure, a breakdown in communication between the three parties and a failure in the regulation system and to monitor the teratogenic effects caused by Valproate.
- On the 8<sup>th</sup> February 2016 the MHRA released new warnings about the dangers of Valproate in child bearing years. A letter was sent out from the Pharmacovigilance Director expressing concern about Valproate and stated that the drug should not be prescribed unless every other option had been exhausted.  
However, INFACT is aware that this information did not reach the vital departments to ensure the warnings reached either the patient or the pharmacist.
- We are aware that neither the Patient Guidance supposed to be given by the GP, or the Patient warning card given by the Pharmacists on collection of prescription arrived at its destination and therefore never reached the patient.
- The MHRA stated it had informed the Clinical Commissioning Groups (CCG's) of such information, however we are aware that this information was not filtered down through the system.

We believe that these instructions and warnings, as the new ones issued earlier last year (Feb 2016) should be made a Mandatory Action to ensure women receive the warnings and stop innocent children being damaged when alternatives and changes can be put in place to avoid it. It has proved apparent that an Incentive Based Structure does not always work.

The above points certainly show that the current system is not fit for purpose and that a new regime of regulation and monitoring of prescription drugs is required in the UK.

It also shows the necessity for a Care Plan to be put in place for the sufferers of Valproate for their future years, and a lump sum offered for the years of suffering they and their families have endured due to the damaging process they have experienced because of the lack of information offered to them.



The Timeline of Events of  
Sodium Valproate (EPILEM)  
From 1972 - 2018  
The Independent Fetal Anti-Convulsant Trust

## INTRODUCTION

The anti-convulsant drug Sodium Valproate, mainly used for Epilepsy, but since the mid 2000's has also been prescribed for conditions such as Migraine, Bipolar and as a pain relief, is widely known, by certain healthcare professionals for causing Fetal Valproate Syndrome and, recently researched, Autistic Spectrum Disorders.

Sodium Valproate has had its licence to be prescribed since 1973, however, even though the pharmaceutical company, Sanofi, were aware of its teratogenic effects on animals before the licence was issued, these important factors were not issued to the healthcare professionals prescribing it until it appeared in the British National Formulary in 1991.

This timeline shows the introduction of Sodium Valproate (Epilim) and the dates of its issue from Sanofi in 1972 to present date, and the delay which has allowed a possible 20,000 people to be affected by its teratogenic effects during pregnancy, with 400 exposed each year to date.

### Timeline of Major Events:

- Restricted license granted in the UK 1972 for Epilepsy Clinics only
- Full license granted and Introduced onto the UK market in 1973 by Reckett & Coleman
- Committee for Safety of Medicines (CSM) discussed and decisions made on the instruction given to Doctors in 1973
- A Datahseet was produced in 1974 by Reckett & Coleman explain the teratogenic effects of the drug
- Sanofi reported teratogenic effects in animals to the Association of the British Pharmaceutical Industry in 1979
- Medical research papers began to appear in the medical journals from 1980 (*See research data attached*)
- Current Problems Sheets released by the Committee on Safety of Medicines stating the teratogenic effects in human released in January 1983 – 2005

- The first Patient Information Leaflet appeared in the box of Epilim in 1995 from the drug company Sanofi which stated: *'Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly'*
- Committee on Safety of Medicines Meeting Minutes where Valproate in pregnancy was discussed from 1999-2005
- No information concerning teratogenic effects given to patients taking Valproate until 2000 by neither the Dept of Health, NHS or Sanofi
- Information to women of child bearing age about the dangers of Valproate in pregnancy was not given in the Patient Information Leaflets by the drug company Sanofi until 2000, even though the PIL's had been in the boxes since 1995.
- Sanofi claim to have released product information to doctors in 1989
- Sanofi claim to have released patient information in 1989
- British National Formulary entry stating sodium valproate and the increased risk of Neural tube defects when taken in pregnancy in 1991
- First Patient Information leaflet (PIL) released by Sanofi Winthrop appeared in boxes of medication in 1995 stating *'If pregnant please consult your doctor'*
- National Institute of Clinical Excellence (NICE) issued guidelines concerning the warnings and pre-conception counselling for women of child bearing age taking Valproate in 2004
- Patient Information Leaflet (PIL) released by Sanofi stating *'Some babies born to mothers who took Epilim Chrono during pregnancy may develop less quickly than normal. These children may require additional educational support.'* In 2005
- Patient Information Leaflet (PIL) released by Winthrop Pharmaceuticals (but same address as Sanofi) stating *'Some babies born to mothers who took sodium valproate during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support'* in 2010. This was released following the collapse of the Product Liability case in November 2010.
- At the beginning of 2013 a major research was released confirming the neurodevelopmental problems caused in children exposed to Valproate. Over 50% of the children exposed to valproate are affected. 11% by major malformations and 40% by Neurodevelopmental problems.
- In July 2013 INFACT feature on Panorama exposing the syndrome and the dangers of Valproate in pregnancy.
- INFACT called into a meeting with the MHRA in August 2013 to discuss the new information about Valproate in pregnancy and the updating of the Yellow card system.

- In October 2013 the Pharmacovigilance Committee (PRAC) met to discuss Valproate review and EU Referral
- In November 2013 Sodium Valproate update was released from the MHRA giving caution to Healthcare Professionals and Prescribers.
- 10<sup>th</sup> April 2014 the Timetable was set for the Valproate review by the European Medicines Agency (EMA)
- In February 2016 The Valproate toolkit was released to inform doctors of the dangers of Valproate in pregnancy
- 26<sup>th</sup> September 2017 an EMA hearing was held into Valproate after another referral due to new warnings not being used by Drs. INFACT used this as a platform to show the failures of the system and the MHRA.
- In February 2018 INFACT have over 1200 children affected by Valproate in pregnancy, although not all with diagnosis of FVS, some diagnosed with Autistic Spectrum Disorders where exposure have taken place.
- 9<sup>th</sup> February 2018 European Medicines Agency (EMA) released new recommendation through the UK Pharmacovigilance Risk Assessment Committee (PRAC) with *“new measures to avoid Valproate exposure in Pregnancy”*  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2018/03/news\\_detail\\_002929.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002929.jsp&mid=WC0b01ac058004d5c1)
- 21st February 2018 Secretary of State for Health & Social care Jeremy Hunt MP announced the Medicines and Medical Devices Safety Review which included Valproate and that the UK regulatory system *“needs to adapt to a changing environment and to draw intelligently on multiple sources of feedback to protect the safety of patients”*  
<https://hansard.parliament.uk/Commons/2018-02-21/debates/7DA2E2F3-E1E6-40CB-8061-680E0399CA97/MedicinesAndMedicalDevicesSafetyReview>

- **Documentation from Archive Documents**

**Committee for the Safety of Medicines:**

NOT FOR PUBLICATION

Committee on Safety of Medicines

Sub-Committee on Adverse Reactions

21<sup>st</sup> March 1973

Data Sheets (CSM/AR/73/22)

Note by Secretary

- The Committee will recall that at their January meeting the desirability of reminding doctors of well-known adverse reactions from time to time was discussed, although no conclusions were arrived at on the best means to achieve this.....
- The Committee may perhaps find that the requirement to supply data sheets meets the need to ensure that all members of the professions are personally informed (and reminded) of possible hazards. The Regulation, incidentally allow for the compilation of a compendium in place of loose data sheets. The ABPI has undertaken to produce such a compendium...
- Other Business  
Data Sheets (CSM/AR/73/22)

In February copies of the Medicines (Data Sheet) Regulations 1972 had been circulated for the information of members together with copies of guidance notes on the sheets..

NOT FOR PUBLICATION

Committee on Safety of Medicines  
Sub-Committee on Adverse Reactions  
16<sup>th</sup> May 1973  
CSM/AR/73  
4<sup>TH</sup> Meeting

8. Anticonvulsant Teratogenicity (CSM/AR/73/28)

Before the Committee was a letter in which the Manufacturer of Mysoline has notified their intention to include information about the possibility that anticonvulsants may be teratogenic in the relevant data sheet and product literature. The Committee welcomed this action and expressed appreciation of ICI's voluntary co-operation. They recommend that the licensing authority should be advised to require that a similar statement is included in all data sheets for anticonvulsants.

28<sup>th</sup> June 1973

Minute 9 of 73/6

3.3. Anticonvulsant Teratogenicity

"The Committee was informed that the Sub Committee on Adverse Reactions had accepted the Main Committee's view that it would be best not to mention the possibility of congenital abnormality following the use of anticonvulsants in relevant packaging inserts. The Sub Committee had still felt, however there was a case for a mention to be made in data sheets to ensure that doctors were aware of the hazard, in part because of the possibility of litigation.

Whilst the Committee was sympathetic to this view they thought in practice it would be extremely difficult to make certain that the statement was included in all the relevant data sheets for the wide range of products containing anticonvulsant substances.

There was the added complication that for substances such as Phenobarbitone there was little or no promotional activity on the part of the manufacturer and thus little likelihood of data sheets for products containing them. As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard, and that in the light of this the Sub-Committee would not consider it necessary to press for any further action."

July 1973

Minute 3.3.73/7

Anticonvulsant Teratogenicity

"The Chairman reminded the Committee of the Sub-Committee's recommendation that all anticonvulsants should have an associated warning regarding possible teratogenicity. The

Committee's views regarding the difficulties this presented had been conveyed to the Sub-Committee but they still felt the evidence sufficiently strong to call for some action on the matter.....

The SUB-Committee would be submitting for consideration a report on the results of their survey...

Publication of the report would help to draw attention to the hazards of anticonvulsant treatments. The Chairman said that he had, however, discussed the matter with Sir Richard Doll who had thought some earlier publicity would be welcomed by his Sub-Committee. He had therefore agreed to discuss the question of how this might best be achieved with Dr Cameron of the BMA, with a view to ensuring that all doctors were alerted to the hazards, yet without creating undue alarm."

NOT FOR PUBLICATION

Committee on Safety of Medicines

Sub-Committee on Adverse Reactions

18 July 1973

CSM/AR/73/4<sup>TH</sup> Meeting

Anticonvulsant Teratogenicity

Minute 8 of 73/3

"The chairman was informed that the Main Committee has also welcomed the action by ICI Ltd, but had thought the evidence not sufficiently conclusive to require all other manufacturers of anticonvulsant products to use a similar statement, especially as it could give rise to fruitless anxiety.....

Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that proposed by ICI could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients themselves seeing it."

Data Sheet

Produced by Reckett & Coleman

June 1974

PRECAUTIONS - WOMEN OF CHILDBEARING AGE

In animals, this compound has demonstrated teratogenic properties in laboratory experiments. Any benefit from its use should be weighed against the possible hazard suggested by this finding.

Standard teratological studies suggest that other anticonvulsants such as phenytoin may have some adverse effect on foetal development. In view of this, care should be taken in prescribing all anticonvulsant compounds including Epilim to epileptic women who may become pregnant

**Association of the British Pharmaceutical Industry (ABPI)**

**Data Sheets Compendium 1979 - 80:**

Reckitt-Labaz

Reckitt & Coleman Pharmaceutical Division

Dansom Lane

Hull

HU8 7DS

EPILIM:

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

**Data sheets Compendium 1980 – 81**

Reckitt-Labaz

Reckitt & Coleman Pharmaceutical Division

Dansom Lane

Hull

HU8 7DS

EPILIM:

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

**Data sheets Compendium 1983 -84**

EPILIM:

Labaz

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

**ABPI Data Sheet Compendium 1985 – 86**

EPILIM:

Labaz

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

**ABPI Data Sheet Compendium 1986 - 87**

EPILIM:

Labaz

*'Women of childbearing age: Valproic Acid or sodium valproate, like certain anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age the benefits of*

*these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.'*

**ABPI Data Sheet Compendium 1989 – 90**

With The Code of Practice for the Pharmaceutical Industry

EPILIM:

Sanofi

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

**ABPI Data Sheet Compendium 1990 – 91**

With The Code of Practice for the Pharmaceutical Industry

EPILIM:

Sanofi

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

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

**ABPI Data Sheet Compendium 1991 - 92**

With The Code of Practice for the Pharmaceutical Industry

EPILIM:

Sanofi

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

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

**ABPI Data Sheet Compendium 1993 - 94**

**With The Code of Practice for the Pharmaceutical Industry**

**EPILIM:**

**Sanofi Withrop**

*'Women of childbearing age: An increased incidence of congenital abnormalities ( including facial dysmorphia, neural tube defects and multiple malformations) have been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.*

*The incidence of neural tube defects in women receiving Valproate neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound and if indicated amniocentesis.*

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

**ABPI Data Sheet Compendium 1994 – 95**

**With The Code of Practice for the Pharmaceutical Industry**

**EPILIM:**

**Sanofi Withrop**

*'Women of childbearing age: An increased incidence of congenital abnormalities ( including facial dysmorphia, neural tube defects and multiple malformations) have been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.*

*The incidence of neural tube defects in women receiving Valproate neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.*

*The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.*

*Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.*

**ABPI Data Sheet Compendium 1995 - 96**

**With The Code of Practice for the Pharmaceutical Industry**

**EPILIM:**

**Sanofi Withrop**

*'Women of childbearing age: An increased incidence of congenital abnormalities ( including facial dysmorphism, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.*

*The incidence of neural tube defects in women receiving Valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.*

*The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.*

*Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.*

**ABPI Data Sheet Compendium**

**And Summaries of Product Characteristics 1996 -97**

With The Code of Practice for the Pharmaceutical Industry

EPILIM:

Sanofi Withrop

*'Women of childbearing age: An increased incidence of congenital abnormalities ( including facial dysmorphism, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with Epilepsy both untreated and treated including those treated with Sodium Valproate.*

*The incidence of neural tube defects in women receiving Valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs. However, there is no reason to contra-indicate folic acid in these women.*

*The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used as abnormal pregnancy outcome tends to be associated with higher total daily dosage.*

*Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement and ultrasound other techniques if appropriate.*

**ABPI Data Sheet Compendium**

**And Summaries of Product Characteristics 1998 - 99**

With The Code of Practice for the Pharmaceutical Industry

EPILIM:

Sanofi Withrop

Pregnancy and Lactation: An increased incidence of congenital abnormalities (including facial dysmorphism, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in the offspring born to mothers with Epilepsy both untreated and treated, including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasound and other techniques if appropriate.

## **Committee on Safety of Medicines**

### **Current Problems Sheets**

#### **No. 9 January 1983**

#### **Sodium Valproate (Epilim) and Congenital Abnormalities**

*'Almost all surveys show a two to three fold increase in the incidence of congenital anomalies among babies born to epileptic women. The most frequently occurring defects, in 2285 children exposed to anticonvulsant therapy in utero were cleft lip with or without palate (3.0%), skeletal anomalies (1.9%), congenital heart disease (1.4%), Central nervous system CNS defects (1.2%), anomalies of the gastro-intestinal tract (1.1%), facial and ear abnormalities (1.0%), mental retardation (0.7%), genito-urinary anomalies (0.6%). Other isolated anomalies occurred. The risk to a woman with Epilepsy, who is receiving an anticonvulsant, of delivering a malformed child is thus about one in ten. Nevertheless, withdrawal of anticonvulsants is not generally advisable because fetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves.'*

*'The malformations reported to occur with Valproate are similar to those with other anticonvulsants, namely neural tube defects, congenital heart lesions, digital anomalies and oral clefts. The recent recommendations that 'newer' drugs such as Valproate may be the drugs of choice for treating epileptic women cannot be accepted uncritically. A new drug may only appear less hazardous because evidence of hazard has not accumulated'*

## **Committee on Safety of Medicines**

### **Current Problems in Pharmacovigilance**

#### **Volume 19**

#### **June 1993**

*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 this drug 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).

**Committee on Safety of Medicines**  
**Current Problems in Pharmacovigilance**  
**Volume 23**  
**September 1997**

Drug-Induced Birth Defects

*'A teratogen is an agent which causes structural or functional abnormalities in the fetus, or in the child after birth. In the UK the proportion of spontaneous abortions in clinically recognised pregnancies is 10-20% and of gross malformations is estimated to be about 3%. The cause of most malformations is not known but at least 2-4% are due to drugs or chemicals.*

Known teratogenic drugs

*The well known teratogenic effects of thalidomide provided the main stimulus for the introduction of modern drug regulation, including the Yellow Card Scheme. Other commonly recognised teratogenic drugs include androgens, cytotoxic agents, lithium, retinoids and warfarin. Drugs should only be prescribed in pregnancy if the benefits for both mother and unborn child outweigh the risks. For example in women with a history of epilepsy, prescription of potentially teratogenic anticonvulsants is often required to prevent seizures, which may be associated with hypoxic CNS damage to the fetus, or in-uterine death. Appendix 4 of the British National Formulary provides a valuable source of information on drugs and pregnancy.*

Detecting potential teratogens

*During development, drugs undergo studies in animals to assess their potential as teratogens. However, lack of a teratogenic effect in animals does not guarantee safety in human pregnancy. Once a drug is marketed, the Yellow card Scheme is an important method for generating signals which then can be more formally investigated. A further data collection system in the UK is the National Teratology Information Service . This service follows up enquiries regarding patients who have received newly introduced drugs, known or suspected teratogens, or who have been exposed to occupational and environmental chemicals while pregnant, to obtain data on pregnancy outcome.*

Assessing Causality

*Confirming that a drug is a teratogen may be difficult. Epidemiological studies can provide quantitative estimates of the strength and statistical significance of associations between drug exposure in pregnant women and congenital abnormalities. Such studies were used to*

*confirm the associations between pre-natal exposure to diethylstilboestrol and vaginal and cervical abnormalities including vaginal adenocarcinoma in female offspring.*

Epidemiological studies have several limitations. For example, the maternal disease requiring drug treatment may itself have resulted in the observed association. Spurious associations can occur or important risks may be missed in investigations involving small numbers of affected patients. Furthermore, women who have had a child with a birth defect are more likely to remember the drugs taken during pregnancy than women who have had a normal child. Assessment of the teratogenicity of a drug must be made therefore on the basis of the reproducibility, consistency and biological plausibility of the combined experimental, clinical and epidemiological data.

### **Committee on Safety of Medicines**

#### **Current Problems in Pharmacovigilance**

#### **Volume 29**

#### **September 2003**

*'The risk of congenital malformations in infants born to mothers receiving anti-epileptic medications is approximately 2 to 3 times higher than in the general population. An increased incidence of congenital malformations (including facial dysmorphism, hypospadias, and multiple malformations, particularly of the limbs) has been demonstrated in infants born to mother with Epilepsy taking Sodium Valproate.*

*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 is the anti-epileptic of choice in patients with certain types of epilepsy such as generalised epilepsy with or without myclonus or photosensitivity.*

*Following a review of the available data, including data from the UK Pregnancy and Epilepsy Register, CSM has advised the following:*

- *Women of childbearing potential should not be started on sodium Valproate without specialist neurological advice.*
- *Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the fetus.*
- *If taken during pregnancy sodium valproate should be prescribed as monotherapy at the lowest effective dose, in divided doses and if possible as a prolonged released preparation.*
- *Folate supplementation prior to pregnancy may reduce the incidence of neural tube defects in infants born to women at high risk. Women should take 5mg folic acid **as soon as contraception is discontinued.***

**British National Formulary**  
**Sodium Valproate/Epilim**

The teratogenic effects of valproate in pregnancy was not reported on, in the BNF between the dates of its first licence in 1973 and March 1991.

BNF Number 21  
March 1991

*Appendix 4: Pregnancy (p478)*

*Valproate (1, 3):  
Increased risk of Neural tube defects (screening advised); neonatal bleeding and hepatotoxicity also reported.*

BNF Number 24  
September 1992

*Appendix 4: Pregnancy. (p516)*

*Valproate (1, 3)  
Increased risk of neural tube defects (screening advised); neonatal bleeding and hepatotoxicity also reported.*

*Increased risk of Neural tube defects (screening advised); Important: see p216); Neonatal bleeding (related to hypofibrinaemia) and hepatotoxicity also reported. See also Antiepileptics.*

*P216.  
Pregnancy and Breastfeeding:*

*In view of the increased risk of neural tube and other defects associated, in particular with Carbamazepine, 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 (alpha-fetoprotein measurement and a second trimester ultrasound scan).*

*To counteract the risk of neural tube defects adequate folate supplements are advised for women before and during pregnancy; to prevent occurrence of neural tube defects, women*

*should receive folic acid 5mg daily, this dose may also be appropriate for women receiving established antiepileptic drugs.*

BNF Number 57

March 2009

*Appendix 4: Pregnancy. (p836)*

*Valproate (1, 3)*

*Increased risk of congenital malformations and development delay (counselling and screening advised – **important**: see p250); neonatal bleeding (relating to hypofibrinaemia) and neonatal hepatotoxicity also reported.*

*P.250*

*Pregnancy and Breastfeeding:*

*There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (reduced if treatment is limited to a single drug). 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 **ante-natal screening** (alpha-fetoprotein measurement and a second trimester ultra-sound scan).*

*To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy ( section 9.1.2)*

*The concentration of antiepileptic drugs in the blood can change during pregnancy, particularly in the later stages. The dose of antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.*

*Routine injection of vitamin K (section 9.6.6) at birth effectively counteracts any antiepileptic-associated risk of neonatal haemorrhage.*

### **Sanofi - Patient Information Leaflets**

- **Sanofi Winthrop (1995) batch number 305/028.**

States:

- a) Are you pregnant or likely to become pregnant?
- b) Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

- **Sanofi Pharma (1996) batch number 510342.**

States:

- a) Are you pregnant or likely to become pregnant?
- b) Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

- **Sanofi-Synthelabo (2001) batch number 30504302**

States:

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3

months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with SPINA Bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with Spina Bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

- Sanofi- Synthelabo (2005) batch number 30504305  
Epilim

#### Information for Women who could become pregnant

Before you start treatment, your doctor should discuss with you the problems that may arise if Epilim is used in pregnancy.

Unplanned pregnancy is not desirable in women receiving Epilim. You should use an effective method of contraception and consult your doctor before planning pregnancy.

Epilim has no effect on how well your oral contraceptive pill works.

It is known that women receiving Epilim during pregnancy have a higher risk that other women of giving birth to a child with an abnormality. The likelihood of abnormalities is increased if you are also taking antiepileptic medicines at the same time. These effects include:

Head and facial deformities including cleft palate – a gap or depression in the lip

Deformities of the bones including dislocation

Malformations of the limbs

Deformities of the urogenital tract including defects in the wall of the male urethra or vagina leading to an additional opening.

Cardiovascular malformations, including heart defects

Defects in the lining of nerve tubes, such as holes or protrusions

Spina Bifida

Women who take Epilim during pregnancy may be more likely to have a baby with Spina Bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with Spina Bifida. There is also an increased risk of other birth defects. These can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support.

There may also be blood clotting problems (such as blood not clotting or not clotting very well) in the new born babies of mothers who have taken Epilim during pregnancy. This may appear as bruising or a delay in the stoppage of bleeds.

It is important not to stop your Epilim suddenly as this is likely in a relapse of your symptoms.

#### Information for Women who are planning to get Pregnant.

If you become pregnant or think you may be pregnant whilst taking Epilim, you must tell your doctor immediately. Consult your doctor before planning pregnancy in order to receive appropriate counselling and to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy. It is essential that you discuss your treatment with your doctor well before you become pregnant.

[Sanofi Aventis \(09. 2007\) batch number 30516303 685](#)

[Epilim Chrono \(slow release\)](#)

#### **Pregnancy and Breast-feeding**

##### **Women who could become pregnant.**

Before you start taking Epilim Chrono your doctor should discuss with you the possible problems when it is taken in pregnancy.

- Unplanned pregnancy is not desirable in women taking Epilim Chrono.
- **You should use an effective method contraception and talk to your doctor before planning pregnancy.**

Epilim Chrono has no effect on how well the oral contraceptive pill works.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:

- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation.
- Malformations of the arms and legs
- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place.
- Heart and blood vessel malformations with heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called Spina Bifida.

Women who take Epilim Chrono during pregnancy may be more likely to have a baby with Spina Bifida. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with Spina Bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim Chrono may have babies with blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.

Some babies born to mothers who took Epilim Chrono during pregnancy may develop less quickly than normal. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim Chrono if you want to become pregnant. Do not stop taking Epilim Chrono suddenly, as it is likely that your fits will come back.

**Women who are planning to get pregnant.**

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim Chrono, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose.
- He or she will also want to check your progress while you are pregnant.

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Winthrop Pharmaceuticals  
(Revised April 2010) Batch Number 31942706 251  
(P O Box 611 Guilford Surrey GU1 4YS  
(Same address as Sanofi)

Sodium Valproate:

**Pregnancy and Breast-feeding**

**Women who could become pregnant.**

Before you start taking Sodium Valproate your doctor should discuss with you the possible problems when it is taken in pregnancy.

- Unplanned pregnancy is not desirable in women taking Sodium Valproate.
- **You should use an effective method contraception and talk to your doctor before planning pregnancy.**

Sodium Valproate has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy and epilepsy with your doctor and, if you have one, your epilepsy specialist. This is to make sure that you and your doctor agree that you should have Sodium Valproate if you become pregnant.

Women taking sodium Valproate during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other anti-epileptic medicines at the same time. The abnormalities include:

- Head and face deformities including cleft palate, a gap or depression in the lip.
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tubes from the bladder to the penis or vagina, with an additional opening being formed.
- Heart and blood vessels malformations with heart defects.
- Abnormalities in the lining of nerve tubes with holes or protrusions
- Spina Bifida

Women who take sodium valproate during pregnancy may be more likely to have a baby with spina bifida. This is an abnormality of the spinal cord. **Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with Spina Bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take sodium valproate may have babies with blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or a bleeding which takes a long time to stop.

Some babies born to mothers who took sodium valproate during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before stopping taking sodium valproate if you want to become pregnant. It is important not to stop your sodium valproate suddenly, as it is likely that your fits will come back.

### **Women who are planning to get pregnant**

If you become pregnant, think you may be pregnant or plan to become pregnant while taking sodium valproate, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

[Sanofi Aventis \(01. 2011\) Batch Number 678326  
Depakote –Valproic Acid \(as Valproate semisodium\)](#)

### **Pregnancy and Breast-Feeding**

You should not take this medicine if you are pregnant or a woman of childbearing age unless explicitly advised by your doctor.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast feeding.

### **Women who could become pregnant**

Before you start taking Depakote, your doctor should discuss with you the possible problems when it is taken in pregnancy.

- Unplanned pregnancy is not desirable in women taking Depakote
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.**

Depakote has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Depakote if you become pregnant. Women taking Depakote during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time..

These abnormalities include:

- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations with heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina Bifida'

Women who take Depakote during pregnancy may be more likely to have a baby with spina bifida.

**Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with Spina Bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Depakote may have babies with blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time stop.

Some babies born to mothers who took Depakote during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

### **Women who are planning to get pregnant**

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Depakote, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant.

It is very important that you discuss your treatment with your doctor well before you become pregnant.

Sanofi Revised (11. 2012.) Batch Number 30514209 815

### Epilim Gastro-resistant tablets

#### **Pregnancy and breast-feeding**

##### **Women who could become pregnant**

**You should not take this medicine if you are pregnant or a woman of child bearing age unless explicitly advised by your doctor.**

Before you start taking Epilim, your doctor should discuss with you the possible problems when it is taken in pregnancy.

- Unplanned pregnancy is not desirable in women taking Epilim
- **You should use an effective method of contraception and talk to your doctor before planning pregnancy.**

Epilim has no effect on how well the oral contraceptive pill works.

Well before you become pregnant it is important to discuss pregnancy with your doctor and, if you have one, your specialist. This is to make sure that you and your doctor agree that you should have Epilim if you become pregnant.

Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time..

These abnormalities include:

- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations including heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called 'Spina Bifida'
- Malformations of the Urethra

Women who take Epilim during pregnancy may be more likely to have a baby with spina bifida.

**Taking folic acid 5mg each day as soon as you stop contraception may lower the risk of having a baby with Spina Bifida.**

There is also an increased risk of other birth defects. These other defects can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim may have babies with:

- Blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop
- Hypoglycaemia (low blood sugar)
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).

Some babies born to mother who took Epilim during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.

Talk to your doctor before you stop taking Epilim if you want to become pregnant. Do not stop taking Epilim suddenly, as it is likely that your fits will come back.

### **Women who are planning to get pregnant**

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant.

It is very important that you discuss your treatment with your doctor well before you become pregnant.

- The problem with Patient Information Leaflets over the years has been where the Pharmacy has not included them in all boxes of Valproate, especially the White chemist box.

### **Summary of Product Characteristics**

#### **Date of approval/revision:**

**September 1997**

#### **Pregnancy and Lactation**

An increased incidence of congenital abnormalities (including facial dysmorphism, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with Epilepsy both untreated and treated, including those treated with Sodium Valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1 – 2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contra-indicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-fetoprotein measurement, ultrasounds and other techniques if appropriate. There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndromes related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers. Platelet count, fibrinogen, plasma level and coagulation status should be investigated in neonates.

**Date of Revision of the text:**

**October 2006**

**Use during pregnancy and lactation**

Women of childbearing potential should not be started on Epilim without specialist neurological advice.

Adequate counselling should be made available to all women with Epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1). Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.

Epilim is the antiepileptic of choice in patients with certain types of Epilepsy such as generalised epilepsy and myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.

If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate. When Epilim treatment is deemed necessary, precaution to minimize the potential teratogenic risk should be followed (see also section 4.6.1 paragraph entitled "In view of the above".)

**4.6.1 Pregnancy**

From experience in treating mother with Epilepsy, the risk associated with the use of Epilim during pregnancy has been described as follows:

• **Risk associated with epilepsy and antiepileptics**

In offspring born to mothers with Epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to Epilim and a risk of developmental delay. Developmental delay has been reported in children born to mother with Epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

**Risk associated with Valproate**

In animals: Teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual does are associated with neural tube defects.

In Humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 – 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with Epilepsy treated with Valproate. Some data from studies, of women with Epilepsy, have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

**In view of the above data:**

When woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, Epilim anti-epileptic treatment should not be discontinued if it has been affective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see section 4.4 Special Warning and Special Precautions for use).

**Risk in the neonate:**

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the Vitamin K factors induced by Phenobarbital and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

**Monthly Index of Medical Specialities (MIMS)**

- June 1998 – September 2001  
There was no record of SPC's for Sodium Valproate or of fetal abnormalities listed in the MIMMS between 1998 – 2001.

### Other Brochures reporting Valproate in Pregnancy:

- BMA New Guide to Medicines and Drugs 1988

Pregnancy: Not usually prescribed. May cause abnormalities in the unborn baby. Discuss with doctor.

- The Martindale – The Extra Pharmacopoeia. 29<sup>th</sup> Edition January 1988

Although congenital malformations have been reported in infants born to women who had received antiepileptic agents including Valproic acid during pregnancy the direct causal role for some of these drugs has been debated due to the fact that combined therapy was often employed. For some references to individual case reports (see below) and for the pregnant epileptic patient see the section on Epilepsy under the uses and administration of Phenytoin.

A review of the adverse effects of Valproate – D. M. Turnbull, Adverse Drug React. Ac. Pois. Rev., 1983, 2.

#### PREGNANCY AND THE NEONATE:

*Pooled data from 13 study groups showed that neural tube defects occurred in 6 of 393 infants exposed to valproic acid compared to 6 of 1718 infants exposed to other antiepileptic agents. It was concluded that this collaboration study confirmed that exposure to Valproic Acid in the first trimester of pregnancy is causally associated with a considerably increased risk of neural tube defects and that the use of Valproic Acid during pregnancy should be avoided.*

*D. Lindhout and D. Schmit (letter) Lancet 1986, 1, 1393.*

Major Research/Journal papers reporting Valproate and the Effects on the Foetus:

**Time line: Key publications which altered the way we think about Valproate exposure.**

**1980-** Dalens, B. Teratogenicity of valproic acid. The Journal of Pediatrics 1980; 97(2):p332-333. The first report of an infant with major congenital malformations thought to be linked to exposure to sodium valproate.

**1982** –Rovet, E. & Guibaud, P. Maternal valproic acid and congenital neural tube defects. The Lancet 1982; 2(8304): p937. – Demonstrates the potential association between prenatal exposure to VPA and spina bifida.

**1988** –Ardinger, H., et al Verification of the Fetal Anticonvulsant Syndrome. American Journal of Medical Genetics 1988; 29:p171-185– the first group case series of children exposed prenatally to sodium valproate and highlights potential characteristics of the syndrome.

**1995** – Clayton-Smith, Donna D. Confirmation of Fetal Valproate Syndrome. Journal of Medical Genetics 1995; 32: p724-727 – The first paper to confirm the affects of Valproate in pregnancy and that of Fetal Valproate Syndrome.

**1996** – King, P.B., et al. Spina bifida and cleft lip among newborns of Norwegian Women. American Journal of Public Health 1996; 86(10):p1454-1457. Demonstrated that changes in anticonvulsant use across the country lead to an alteration in the type of birth defects seen in the children.

**1997** – Samren, E.B., 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; 38(9): p981-990. This collaboration of a number of different research groups highlights the importance of the dose of the drug.

**2000-** Moore, S., et al. A clinical study of 57 children with fetal anticonvulsant syndromes. Journal of Medical Genetics 2000;37:p489-497. The first study into a group of children diagnosed with fetal anticonvulsant syndromes.

**2001** –Adab, N., et al. The longer term outcome of children born to mothers with epilepsy. Journal of Neurology, Neurosurgery and Psychiatry 2004; 75:p1575-1583. The first study to include a large group of children exposed to sodium valproate and to find that they require increased levels of educational support.

**2004-** Gaily, E., et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004; 62:p28-32. This large and well designed study found that the IQ of children exposed to carbamazepine was not significantly different from a group of un-exposed children.

**2006-**Hunt, S., et al. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2006; 67: p1876-1879. The first investigation into prenatal exposure to levetiracetam (Keppra) and birth defects.

**2008** –Hunt, S., et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008; 71: p272-276. The first paper to investigate prenatal exposure to topiramate.

**2008** – Bromley, R., et al. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008; 71: p1923-1924. The first prospective study to demonstrate an increased prevalence of autistic spectrum disorders in children exposed to sodium valproate.

**2009**- Meador, M., et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *The New England Journal of Medicine* 2009; 360(16): p1597-1605. The largest prospective study into sodium valproate and lamotrigine demonstrating that the first is associated with reduced IQ.

**2011** –Shallcross, R., et al. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 76; p383-389. The first study to investigate the rate of developmental delay in a group of children exposed to levetiracetam.

**2011**- Tomson, T., et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurology* 2011; 10: p609-617. The largest study to date which shows level of risk by dose of antiepileptic drug.

**2013** – Bromley RL., et al. The prevalence of Neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *Neurol Neurosurg Psychiatry* 2013; **0**: p1-7.  
In the context of already published work, suggests that the risks associated with VPA treatment during pregnancy include neurodevelopmental disorders.

It is necessary to note that all the above documentation was made available to Healthcare professionals from 1973 onwards, however they had previous been informed “Not to tell the patient” in 1973.

We believe that Dear Doctor went out to this effect, but has never been found in the Archive. Yet no follow up information, to a new intake of Doctors was ever produced and so were not fully made aware of the dangers or instructed otherwise to pass any information onto the patient.

As time has progressed we have found that Pharmacists, who should have been informing patients by ensuring the Patient Information Leaflets were given in the boxes of Sodium Valproate have also failed in their Duty of Care

However the problem developed with this as boxes of Valproate were only produced by Sanofi as 100 tablet boxes. We are aware that most women are prescribed 1000mg per day and so would be given the 500mg tablet, thus receiving 60 tablets per month and so would receive their medication in the Pharmacy white box without a Patient Information Leaflet inside.

The Valproate Toolkit produced and released in February 2016 was to amend the information women received from their Dr and Pharmacist, however this did not prevail and information failed to reach the patient due to it not being a Mandatory Action sent out by the Medicines and Healthcare Regulatory Agency (MHRA). This is now to take place in March although until then, is an embargoed piece of information.

## Valproate and Foetal Anticonvulsant Syndrome

19 October 2017  
Volume 629

<https://hansard.parliament.uk/Commons/2017-10-19/debates/84D4BB19-D2BF-446A-A249-CD28BD7E8E06/ValproateAndFoetalAnticonvulsantSyndrome>

## Medicines and Medical Devices Safety Review

21 February 2018  
Volume 636

<https://hansard.parliament.uk/commons/2018-02-21/debates/7DA2E2F3-E1E6-40CB-8061-680E0399CA97/MedicinesAndMedicalDevicesSafetyReview>

## **INFACT Case Studies**

*Not included for publication.*

## **National Archive Documents**

(As noted in the Timeline of Events above)

Below are copies of the National Archive Documents uncovered in January 2015 by INFACT.

The documents cover minutes in meetings held by the Committee for Safety of Medicines from Sub Committees for Adverse Reactions and Toxicity from 1973 giving a clear picture of the instructions given to Doctors at this time and the knowledge already held by the Governing Bodies.

2. MINUTES OF THE MEETING HELD ON 28 JUNE 1973

These were agreed and signed by the Chairman.

3. MATTERS ARISING FROM THE MINUTES

3.1 Jaundice and Erythromycin leaflet (minute 3.1 of 73/6)

The Committee was informed that the leaflet had been distributed on 18 July 1973, but had provoked little reaction.

3.2 Consideration of Applications (Minute 4 of 73/6) - Ciba-Geigy Ltd - Coranin Ampoules - PL/0008/0110

Members were reminded of their decision that this should be a Section 21(1) case. The licensing authority had however since concluded that an application for a product licence did not appear necessary and the matter was being taken up with the company with a view to the application being withdrawn. In these circumstances the Chairman said he had agreed that the action proposed by the Committee should be held in abeyance; but the question of indications for products of this kind would be borne in mind to be brought up again in the course of review of product licences of right.

3.3 Anticonvulsant Teratogenicity (minute 9 of 73/6)

The Committee was informed that the Sub-Committee on Adverse Reactions had accepted the Main Committee's view that it would be best not to mention the possibility of congenital abnormality following the use of anticonvulsants in relevant package inserts. The Sub-Committee had still felt, however, there was a case for a mention to be made in data sheets to ensure that doctors were aware of the hazard, in part because of the possibility of litigation. Whilst the Committee was sympathetic to this view they thought in practice it would be extremely difficult to make certain that the statement was included in all the relevant data sheets for the wide range of products containing anticonvulsant substances.

There was the added complication that for substances such as phenobarbitone there was little or no promotional activity on the part of the manufacturers and thus little likelihood of data sheets for products containing them. As the matter had been mentioned in the Chairman's letter sent to all doctors in May 1973 the Committee felt that reasonable steps had already been taken to see that the profession was alerted to the hazard, and that in the light of this the Sub-Committee could not consider it necessary to press for any further action.

#### 3.4 Podophyllin Preparations (minutes 10 of 7/6)

It was reported that the Committee's recommendation that podophyllin preparations should be included in the Prescription Only list had been conveyed to the Secretary of the Medicines Commission.

#### 3.5 Notes for Guidance in Reproductive Studies (minutes 11 of 7/6)

The Committee was informed that copies of these notes had been sent to ABPI, IACG and to Dr Fairweather (For CONA II) inviting comments.

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## COMMITTEE ON SAFETY OF MEDICINES

## SUB-COMMITTEE ON ADVERSE REACTIONS

Minutes of the Meeting held on 18 July 1973

## Present:

Sir Richard Doll (Chairman)  
 Professor W I Cranston  
 Dr D M Davies  
 Professor D J Finney  
 Professor R H Girdwood  
 Dr M J Linnett  
 Professor W W Mushin  
 Professor D A Price Evans  
 Professor D W Vere  
 Mr F A S Middleton (Secretary)

Dr W H W Inman )  
 Dr M F Cuthbert ) Professional  
 Dr G Greenberg ) Secretariat  
 Dr A B Wilson )  
 Mr A T Gray )

## Also Present:

Mr R E Tringham DHSS  
 Dr A T B Moir SHHD  
 Dr E L Harris )  
 Dr A J Taylor ) Committee  
 Miss M Edington ) Secretariat

Contents

1. Apologies for absence
2. Minutes of the Meeting held on 16 May 1973
3. Matters arising from the minutes
4. Professional Secretariat's Report
5. Sudden Deaths and Phenothiazines
6. MAOI's and Tricyclic Antidepressants
7. Interactions between MAOI's and L-Tryptophen
8. Visual Disturbances with Ospolot
9. Dangers of Corn Starch in Aural Insufflation
10. Tetracyclines and Tooth Discolouration
11. Review of Recommendations
12. Adverse Drug Interactions booklet
13. Drug Dictionaries
14. Maxolon - dosage recommendations
15. Reports of Ocular Adverse Reactions
16. Advice from outside experts
17. Breast Atrophy and Oestrogen Therapy
18. Items for information
19. Date and time of next meeting

3.9 Drug Formulations (Minute 7 of 73/3)

The Chairman reported that the Main Committee had considered Mr Barrett's paper and had also commented on the difficulties associated with the problems to which Mr Barrett has drawn attention. They had decided to refer the paper to the Sub-Committee on Chemistry and Pharmacy for their consideration also, with a view to consultation with the ABPI on what might be done; one possibility being a communication to the BMJ on the matter.

3.10 Anticonvulsant Teratogenicity (Minute 8 of 73/3)

The Committee was informed that the Main Committee had also welcomed the action by ICI Ltd but had thought the evidence not sufficiently conclusive to require all other manufacturers of anticonvulsant products to use a similar statement, especially as it could give rise to fruitless anxiety. The Sub-Committee believed, however, that the character of the evidence was strong enough for an assurance to be given to the Main Committee on that account, but accepted the point regarding anxiety. Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that proposed by ICI could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients themselves seeing it.

It was also agreed that a mention could be included in the next letter from Chairmen to all doctors.

BN 116/5

W0012/0001

Valproic Acid

Sodium Valproate

(Anti-Convulsant)

Pharmacia Products Limited

Sub-Committee on Toxicity and Clinical Trials

The Sub-Committee considered a further report on the monitored release of epilim, sodium valproate, which had been submitted following the limited licence initially granted for this product. In view of the results presented, and in particular the further data on teratology the Sub-Committee now recommends as follows:

Recommendations

On the evidence before them the Sub-Committee recommends variation of the product licence to delete the requirement regarding monitoring on condition that the indication for use reads as follows:

"for use in generalised, focal or other epilepsy but only to be used in severe or resistant cases in women of child bearing age"

and that the following warning is included in all literature issued about this product;

"Women of Child Bearing Age"

This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazards suggested by these findings".

Main Committee March 1974

On the evidence before them the Committee advise variation of the product licence to delete the requirement regarding monitoring on condition that the indication for use reads as follows:

"for use in generalised, focal or other epilepsy. In women of child bearing age, it should only be used in severe cases or those resistant to other treatment",

and that the following warning is included in all literature issued about this product;

"Women of Child Bearing Age"

This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings".

The Committee noted that a special directive to designate this product as new was sent with the letter of intent when the original product licence was granted.

## DATA SHEET

### NAME OF PRODUCT

Epilim

### PRESENTATION

Epilim is available as a scored white tablet with a diameter of 11mm.

The active ingredient is Sodium Valproate (200mg per tablet).

### USES

For use in generalised, focal or other epilepsy (e.g. Petit Mal, Grand Mal, Mixed and other Psychomotor epilepsy).

In fertile women inadequately controlled by other therapies, the probable benefits of Epilim should be weighed against the possible hazard during early pregnancy suggested by laboratory experiments in animals (see Precaution Women of Childbearing Age).

### DOSAGE AND ADMINISTRATION

Adults and Children over 15 yrs.

Epilim can be introduced alone or added to existing treatment.

#### New Patients:

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

#### Patients receiving other Therapy:

Treatment should start with 1 tablet twice a day. Dosage can be increased at intervals of three days in increments of two tablets per day; optimum control is achieved usually within the dosage range of 4-7 tablets (800-1,400mg) per day. (However in several recently published controlled trials, it was found that the dose could be increased with advantage to

2.4g per day to achieve control in very severe cases).

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

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

Children under 15 years and Infants.

Dosage should be related to age within the range as follows:

0-3 years: Usually 20-30 mg/kg/day.

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

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

## CONTRA-INDICATIONS AND PRECAUTIONS

### CONTRA-INDICATIONS

There are no specific contra-indications for Epilim but note should be taken of the following precautions.

### PRECAUTIONS - GENERAL

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

### Combined Medication:

Epilim is well tolerated in combination with other anti-epileptic agents.

Epilim may enhance the sedative effects of other agents, particularly barbiturates; this should be recognised when introducing Epilim to existing treatment and may require concomitant reduction in the dosage of other agents. Similarly Epilim, in common with many other medications, may

potentiate the effect of mono-amine oxidase inhibitors (MAOI) and thymoleptics and the doses of these agents should be reduced accordingly.

Diabetic Patients:

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

Overdosage:

Reports of accidental overdosage of Epilim have been rare. Recovery after the ingestion of 3 to 30g has been uneventful following conservative management.

As Epilim is absorbed very rapidly gastric lavage may be of limited value.

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

PRECAUTIONS - WOMEN OF CHILDBEARING AGE

In animals, this compound has demonstrated teratogenic properties in laboratory experiments. Any benefit from its use should be weighed against the possible hazard suggested by this finding.

Standard teratological studies suggest that other anticonvulsants such as phenytoin may have some adverse effect on foetal development. In view of this, care should be taken in prescribing all anticonvulsant compounds including Epilim to epileptic women who may become pregnant.

PRECAUTIONS - PHARMACEUTICAL

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

LEGAL CATEGORY

Prescription only medicine.

PACKAGE QUANTITIES

Carton containing 100 tablets in foil.

FURTHER INFORMATION

Epilim represents a new approach in the therapy of epilepsy. Whereas none of the currently available drugs have chemical features in common, Epilim;

is a different entity with a simple chemical structure which (unlike existing drugs) does not contain nitrogen. Biological studies on Epilim indicate that it may have a different mode of action in that it produces an increase in the level of S-aminobutyric acid (GABA) in the brain by inhibiting GABA Transaminase which is responsible for the breakdown of GABA. Although there is no simple correlation between convulsive activity and GABA levels, evidence linking them is growing.

Clinically Epilim is effective in treatment of Petit Mal, Grand Mal, Mixed Epilepsies, and those with Temporal Lobe (or Psychomotor) components.

PRODUCT LICENCE HOLDER

Reckitt-Labaz

MANUFACTURERS

Reckitt & Colman Pharmaceutical Division,

Hull HU8 7DS

PRODUCT LICENCE NUMBER

0623/0001

DATA SHEET REFERENCE

This Data Sheet was printed in June 1974.

Further information is available on request from:

Reckitt & Colman Pharmaceutical Division

Hull HU8 7DS Tel: 0462 26151

Printed in Britain 'Epilim' is a registered trade mark EP/1/74J

Continued from previous page

#### BEFORE TAKING YOUR MEDICINE

If you have been advised DO NOT take Epilim without first talking to your doctor.

If you are unsure YES to any of the following questions, tell your doctor. He may need to give you special instructions.

Are you pregnant or likely to become pregnant?

Are you diabetic?

Are you taking any other medicines to control your epilepsy?

Are you taking any medicine to reduce blood clotting (eg anticoagulants, aspirin)?

Are you taking antidepressants?

#### TAKING YOUR MEDICINE

Take your medicine regularly, as directed by your doctor. This is particularly important when

adjusting doses to make sure that you are getting the best control from your medicine.

Look at the label on your medicine. It will tell you when to take it. If it does not, or you are not sure, ask your doctor or pharmacist for advice.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the correct time take it as soon as you remember then go on as before.

If you accidentally take an overdose contact your nearest hospital casualty department or tell your doctor immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop, your seizure condition may get worse.

#### AFTER TAKING YOUR MEDICINE

Make sure you keep your regular check-up appointments. They are very important as your dosage may need to be changed.

Fragege into hospital or visit another doctor or a doctor call them you are taking Epilim.

Epilim can affect the liver in a very small number of patients. You should tell your doctor IMMEDIATELY

if you develop a yellowish skin especially if it is within the first six months of treatment and particularly

if it is accompanied by itching, nausea or loss of appetite, jaundice or soreness of your

epilim.

Epilim may sometimes cause some stomach upsets, loss of weight or weight gain. You need only

consult your doctor about these if symptoms become troublesome.

Occasionally Epilim may affect the hair. Any loss of hair is usually temporary but when it grows back it

may be more curly than before.

Epilim can also have other effects. You should report any of the following symptoms to your doctor:

Some stomach pain

Increased thirsting or a tendency to urinate more freely

Dizziness or problems with balance

A rash or anything else which is unusual or unexpected

Epilim may affect your thinking if you become pregnant and by these circumstances it is important to consult your doctor promptly.

#### STORING YOUR MEDICINE

Keep your tablets in a safe place where children cannot reach them; your tablets could harm them.

If your doctor decides to stop the treatment, when any leftover tablets in the pharmacy. Only keep

them if your doctor tells you to.

#### WHAT'S IN YOUR MEDICINE

Epilim (Sodium Valproate) tablets are blue and come in two sizes containing 200mg or 500mg Sodium

Valproate. They contain other and other inactive ingredients including E 01.

This leaflet provides a summary of the information available on your medicine. For further information, consult your doctor or pharmacist.

#### THIS LEAFLET APPLIES TO EPIILIM ENTERIC COATED TABLETS ONLY

**REMEMBER:** This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet has been produced in accordance with guidelines issued by the Association of British Pharmaceutical

Industries.

The product name for Epilim Enteric Coated is SANOFI.

Sanofi UK Ltd

Kenilworth, NJ 07033

England



## What you should know about Epilim® Enteric Coated

Sodium Valproate EP

Please read this carefully before you start to take your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of your medicine is Epilim. It contains Sodium Valproate. This is one of a group of medicines called 'anticonvulsant or anti-epileptic agents' which are used to treat epilepsy.

#### Things to remember about Epilim

1. Before taking your medicine read the back of this leaflet.
2. Take your medicine as directed by your doctor. Read the instructions on the label carefully.
3. Epilim can sometimes cause side effects. See "After taking your medicine" on the back of this leaflet.
4. Do not stop taking your medicine suddenly. Ask your doctor first.
5. Tell medical staff you are taking this medicine, for example, if you go into hospital or see a dentist or another doctor.
6. If you are likely to become pregnant, tell your doctor.

You will find more about Epilim on the back of this leaflet.



## EPILIM® CHRONO CONTROLLED RELEASE

(Sodium valproate/valproic acid)  
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. It you have any questions or are not sure about anything ask your doctor or pharmacist. The name of this medicine is Epilim Chrono Controlled Release tablets.

### WHAT IS IN THIS MEDICINE?

Each Epilim Chrono 200 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 200mg sodium valproate.  
Each Epilim Chrono 300 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 300mg sodium valproate.  
Each Epilim Chrono 500 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 500mg sodium valproate.  
Each tablet contains hydroxylic acid, ethylsuccinate, titanium dioxide (E171), erythrosine (E127), indigo carmine (E132), black iron oxide (E172) and Macrogel 400.  
Epilim Chrono tablets are oval shaped like cigarette tablets and are supplied in cartons of 100.

Epilim Chrono is an antiepileptic.  
Product Licence holder:  
Sanofi-Synthelabo  
PO Box 597  
Guildford  
Surrey

Manufactured by:  
Fawcett Manufacturing Centre  
Edgelyscote Avenue  
Fawcett, Newcastle upon Tyne  
Tyne and Wear  
NE3 3TT

### WHAT IS THIS MEDICINE FOR?

Epilim Chrono is used to treat epilepsy (fits). Epilim Chrono is made so that the medicine in the tablet is released slowly over a long period of time.

### BEFORE TAKING THIS MEDICINE

Epilim should not be taken by patients with:

- liver problems
  - a family history of liver problems
  - a known allergy to Epilim/chronon valproate or any of the other ingredients
  - porphyria (a rare metabolic condition)
- If you have lupus (an inflammatory skin disease), please tell your doctor before taking Epilim.  
Your doctor may wish to do tests before you start your treatment and for the first six months of treatment.

If you are diabetic Epilim Chrono may make urine tests give false results.

### Epilim Chrono and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1.2% chance of having a baby with such a child. This however can usually be decreased in the first part of pregnancy by normally taking tablets. Taking dietary supplements of folic acid may lower the risk of having a baby with spina bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor 30,000.35

you know you are pregnant.

**Breast feeding:** very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim Chrono or the effects of the other

medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, gabapentin, levetiracetam
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, rifampicin and meropenem - antibiotics
- salbutamol - used to prevent asthma
- benzocaine - used as a numbing agent
- benzocaine - used as a numbing agent
- zalcitabine - used to treat HIV and AIDS
- immunosuppressants - used to treat cancer

Taking Epilim with ceftriaxone, which is used to prevent or treat malaria, may make it more likely that you may have seizures. Before travelling you should discuss taking malaria tablets with your doctor or pharmacist.

When you first start taking Epilim or if you are taking it with other medicines you may notice some drowsiness, it affected you should not drive or operate machinery.

### TAKING THIS MEDICINE

Adults:

The usual dose of Epilim Chrono is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

The usual dose will be determined by the doctor.

The usual dose of Epilim Chrono is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Epilim Chrono is not suitable for use in children under 20kg.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim Chrono than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim Chrono your doctor may increase the dose of Epilim Chrono by 5 to 10mg for each kg of body weight per day.

If you have kidney disease your doctor may prescribe a lower dose.

Swallow the tablets whole, do not crush or chew them, with a drink of water, usually after meals.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

### WHILE TAKING THIS MEDICINE

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim Chrono. Epilim can affect the liver (and many) the pancreas in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs or shortness of breath or a general feeling of being unwell. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood (which may cause vomiting, unsteady movements and an awareness of your surroundings); vertigo - inflammation of the blood vessels; you may notice pain, numbness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before. Very rarely it may also cause an increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; abnormal or problems with balance. Rarely it may cause weakness, confusion; hallucinations; seizures; change in mood, jerky muscle movements and loss of consciousness.

Rashes, sometimes severe, occur rarely but patients who are also taking benzotriazine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible so you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in drowsiness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also, tremor disorders have occurred rarely.

Do not take this medicine after the month shown on the pack.

Epilim Chrono tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you use them. Store them in a dry place at less than 30°C.

Date of revision of leaflet: February 2001.

This leaflet does not contain all the information about your medicine. If you have any

questions or are not sure about anything ask your doctor or pharmacist.

The British Epilepsy Association (telephone: 0800 890 5050) will also be happy to try and answer any

general questions on epilepsy.

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**sanofi-synthelabo**

Tell your doctor or pharmacist if any of the following side effects get serious or last longer than a few days, or if you notice any side effects not listed in this leaflet:

- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food or taking the Epilim EC Tablets instead
- Headache
- Skin problems such as rashes. These happen often, but more often in people also taking lamotrigine
- Atrial
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, swelling or increased need to pee after starting treatment

#### Blood tests

Epilim Chrono can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Talk to your doctor or pharmacist if any of the side effects get serious or last longer than a few days, or if you notice any side effects not listed in this leaflet.

#### How to take Epilim Chrono

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date shown on the blister and carton after 24P.

The expiry date refers to the last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of in household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

#### Further information

What Epilim Chrono contains

- Each 200mg controlled release tablet contains a mixture of 133.2mg sodium valproate and 58mg valeric acid, equivalent to 200mg of the active substance sodium valproate
- Each 300mg controlled release tablet contains a mixture of 199.8mg sodium valproate and 87mg valeric acid, equivalent to 300mg of the active substance sodium valproate

- Each white controlled release tablet contains a mixture of 133mg sodium valproate and 14.5mg sodium salt, equivalent to 500mg of the active substance, sodium valproate
- The other ingredients are: hypromellose (E464), ethylcellulose, hydroxyethyl cellulose, titanium dioxide (E171), erythrosine (E129), aluminium lake (E127), indigo carmine aluminium lake (E132), iron oxide black (E172), macrogol 400

What Epilim Chrono looks like and contents of the pack  
Epilim Chrono tablets are oval shaped and blue coloured. The blisters are supplied in blister packs of 100

#### Marketing Authorisation Holder and Manufacturer

Sanofi-Aventis  
One Crutcher Street  
Danbury  
Connecticut  
USA  
Tel: 01483 505515  
Fax: 01483 533432  
email: us-medicalinformation@sanofi-aventis.com

#### Sanofi-Aventis Further Manufacturing Sites

Epilim® Avenue  
Fresno  
Newcastle upon Tyne  
York in West  
NE3 3Y  
UK

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in 09/2007.

#### © Sanofi-Aventis, 2006-2007

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

**Epilepsy Action**, New Acton House, Gate Way Drive, Yeading, (Leeds), LE19 7YJ  
Telephone: 01939 980 5000. Website: www.epilepsy.org.uk

**National Society for Epilepsy (NSE)**, Chesham Lane, Chalfont St Giles, Bucks, HP8 0RQ  
Telephone: 01494 671000. Website: www.epilepsysoc.org.uk

#### PAKAR MARKET INFORMATION FOR THE USER

**Epilim® Chrono 200mg, 300mg and 500mg Controlled Release Tablets sodium valproate**

#### sanofi aventis

Is this leaflet hard to see or read? Phone 01483 505515 for help

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again
- If you have further questions, please ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

#### In this leaflet:

1. What Epilim Chrono is and what it is used for
2. When you take Epilim Chrono
3. How to take Epilim Chrono
4. Possible side effects
5. How to store Epilim Chrono
6. Further information

#### What Epilim Chrono is and what it is used for

What Epilim Chrono is  
Epilim Chrono contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim Chrono is used for  
Epilim Chrono is used to treat epilepsy (fit) in adults and children.

#### When you take Epilim Chrono

Do not take Epilim Chrono and tell your doctor if:

- You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim Chrono (see section 4 - Further information)
- You are on other medicines, such as a birth control pill, or taking any other medicine, including a vaccine, or having any other medical condition, such as a kidney or liver problem, or a history of bleeding problems, swelling of your legs, feet, feet or tongue

- You have liver problems or you or your family have a history of liver problems
  - You have a rare disease called porphyria
- Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim Chrono.

#### Take special care with Epilim Chrono

Check with your doctor or pharmacist before taking this medicine if:

- You have diabetes. This medicine may affect the results of urine tests
  - You have kidney problems. Your doctor will give you a lower dose
  - You have the following: brain disease or a metabolic condition affecting your brain
  - You have a "rare type of blood clot" where too much ammonia builds up in the body
  - You have an illness called "systemic lupus erythematosus" (SLE) - a disease of the immune system which affects skin, bones, joints and internal organs
- If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim Chrono.

#### Weight gain

Taking Epilim Chrono may make you put on weight. Talk to your doctor about how this will affect you.

#### Blood tests

Your doctor may wish to do blood tests before you start taking Epilim Chrono and during your treatment.

#### Taking Epilim Chrono with other medicines

Always tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal remedies for health care. Also some medicines can affect the way Epilim Chrono works.

#### The following medicines can increase the chance of you getting side effects, when taken with Epilim Chrono:

- Some medicines used for pain and inflammation (analgesics) such as aspirin
- Some other medicines used to treat fit (epilepsy) - see page 4, section 3 "Further information and reactions for fit"
- This includes medicines such as phenytoin, phenobarbital, phenylethylamine, carbamazepine, lamotrigine and felbamate

#### Epilim Chrono may increase the effect of the following medicines:

- Medicines used for thinning the blood (such as warfarin)
- Digoxin used to treat fit (epilepsy)
- Tricyclic antidepressants
- Medicines for depression
- Monoclonal antibody inhibitors (MAOI) such as methylenedioxymethamphetamine (MDMA) and selegiline
- Medicines used to calm emotional and mental conditions such as diazepam and alprazolam

#### The following medicines can affect the way Epilim Chrono works:

- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Some medicines used for stomach aches
- Some medicines used for infections (antibiotics) such as ciprofloxacin, metronidazole and erythromycin
- Cimetidine used to lower blood cholesterol levels

#### Pregnancy and breast feeding

Women who could become pregnant

Do not start taking Epilim Chrono, your doctor should discuss with you the possible problems when it is taken in pregnancy.

• Unplanned pregnancy is not desirable in women taking Epilim Chrono

You should use an effective method of contraception and talk to your doctor before planning pregnancy. Epilim Chrono has no effect on how well fit oral contraceptive pills work.

Women taking Epilim Chrono during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormality is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:

- Head and face abnormalities including cleft palate (gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Abnormalities of the arms and legs
- Deformities of the face from the forehead to the neck, where the earwax is located in a different place
- Heart and blood vessel malformations with heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called "spina bifida"

Women who take Epilim Chrono during pregnancy may be more likely to have a baby who gains weight. Taking Epilim Chrono each day as soon as you stop contraception may lower the risk of having a baby with spine defects.

There is also an increased risk of other birth defects. These other defects are usually first detected in the first 3 months of the pregnancy, during routine antenatal screening blood tests and ultrasound scans.

Pregnant mothers who take Epilim Chrono may have babies with blood clotting problems such as blood not clotting or clotting very well. This may appear as bruising or bleeding which takes a long time to stop.

Some babies born to mothers who took Epilim Chrono during pregnancy may develop less quickly than normal. These children may require additional educational support.

Talk to your doctor before you start taking Epilim Chrono if you want to become pregnant. Do not stop taking Epilim Chrono suddenly, as it is likely that your fit will come back.

#### Women who are planning to get pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim Chrono, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.

#### Breast feeding

Very little Epilim Chrono gets into the breast milk. However, talk to your doctor about whether you should breast feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

#### Driving and using machines

You may feel sleepy when taking Epilim Chrono. If this happens to you, do not drive or use any tools or machines. Taking other medicines could increase this or other physical and mental health problems may increase sleepiness.

#### How to take Epilim Chrono

Always take Epilim Chrono exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

#### Taking this medicine

- Your doctor will decide how much Epilim Chrono to give you for your child depending on your or your child's body weight
- Take this medicine by mouth
- Take Epilim Chrono with or after food. This will help to stop the feelings of sickness that may happen after taking Epilim Chrono
- Do not crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

#### How to take this medicine

This medicine can be taken once or twice daily

#### How often to take

**Adults (including the elderly)**  
• The starting dose is 100mg daily. Your doctor will gradually increase this dose by adding every 3 days depending on your condition- The usual dose is generally between 1000mg and 2000mg (20-40mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your dose

#### Children over 10 kilograms

• The starting dose should be 100mg daily. Your doctor should increase this dose depending on your child's illness- The usual dose is between 20mg and 40mg for each kilogram of body weight each day
- This may be increased to 250mg for each kilogram of body weight each day depending on your child's illness

#### Children under 10 kilograms

Epilim Chrono is not recommended in children that weigh less than 10 kilograms. Epilim Chrono (sugar free) or Epilim Chrono is recommended instead.

#### Patients with kidney problems

Your doctor may decide to adjust your or your child's dose

#### Patients taking other medicines for 'fit' (epilepsy)

You or your child may be taking other medicines for epilepsy at the same time as Epilim Chrono. If so, your doctor should gradually increase treatment depending on your fit or your child's condition

Your doctor may increase the dose of Epilim Chrono by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim Chrono than you should, if you take more Epilim Chrono than you should, get a doctor or go to a hospital casualty department straight away. Take the medicine with you. This is so the doctor knows what you have taken

The following effects may happen: feeling sick or being sick, growth of the nose become swollen, dizziness, loss of consciousness, weak muscles and joint aches, breathing problems, headache, fits (seizures), confusion, hearing loss and unusual or inappropriate behaviour

#### If you forget to take Epilim Chrono

If you forget to take a dose, take it as soon as you remember. If it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

#### If you stop taking Epilim Chrono

Stop taking with your doctor tells you to stop. Do not stop taking Epilim Chrono just because you feel better. If you stop your fit may come back

#### Tests

Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim Chrono can change the levels of liver enzymes shown up on blood tests. This can mean that you or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim Chrono.

#### What if you have any further questions on the use of this medicine, ask your doctor or pharmacist

#### Further information

Like all medicines, Epilim Chrono can cause side effects, although not everybody gets them.

#### Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- You have an allergic reaction. This may include a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue

Liver problems and problems of the pancreas may show a yellow tinge which may happen in the last six months of treatment. This happens in a very small number of people taking Epilim Chrono. It includes feeling sick and being sick many times, being very tired, sleep and weak stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling, especially of the legs and feet but also swelling other parts of the body, starting of your fit or general feeling of being unwell

Your doctor may tell you to stop taking Epilim Chrono immediately if you have these symptoms

You have a skin rash or skin lesions with a central ring and a pale centre which may be itchy, sore or bleed with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called "severe cutaneous reaction"

Blurring or bleeding of the skin around the lips, eyes, mouth, nose and genitalia. Also fits like convulsions and loss of fit may be something called "toxic epidermal necrolysis"

Swelling from inside and getting more swollen than usual. This could be a blood problem called "thrombocytopenia". It can also be due to a fall in the number of white blood cells (leucopenia) or another condition that affects and is a low red cell, white blood cells and platelets (pancytopenia)

Blind spotting (vision) (bleeding for longer than usual) bruising or bleeding for longer than usual

Changes in mind, loss of memory, loss of consciousness and deep loss of consciousness (coma)

#### Tell your doctor as soon as possible if you have any of the following side effects:

- Changes in behaviour including being very slow and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fit such as phenytoin are taken at the same time as if the Epilim Chrono starting dose is high or has been suddenly increased
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or very slow
- Feeling shaky (tremor), steps or unsteady when walking or getting muscle movement
- Feeling sick or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blistering with the skin falling away

The Patient Information Leaflets below in PDF can be opened as a separate document when double clicked on:



Epilim PIL  
04.2010.pdf



Epilim PIL November  
2012.pdf



Epilim PIL 2015.pdf



Epilim PIL 2016.pdf

### Research Papers

Dalens, B., Raynaud, E.-J., Gaulme, J (1980) Teratogenicity of valproic acid. *The Journal of Pediatrics* 97(2):332-333 [https://doi.org/10.1016/S0022-3476\(80\)80517-8](https://doi.org/10.1016/S0022-3476(80)80517-8)

Nau, H., Rating, D., Koch, S., Häuser, I., Helge, H. (1981) Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *Journal of Pharmacology and Experimental Therapeutics*. 219 (3): 768-777  
<http://jpet.aspetjournals.org/content/219/3/768>

Winter, R.M., Donnai, D., Burn, J., Tucker, S.M. (1987) Fetal valproate syndrome: is there a recognisable phenotype? *Journal of Medical Genetics* 24:692-695.  
doi: 10.1136/jmg.24.11.692

Clayton-Smith, J., Donnai, D. (1995) Fetal valproate syndrome. *Journal of Medical Genetics* 32:724-727 <http://dx.doi.org/10.1136/jmg.32.9.724>

Bromley, R.L., Mawer, G.E., Briggs, M., et al. (2013) *Journal of Neurology, Neurosurgery, and Psychiatry*. 84:637-643 doi: 10.1136/jnnp-2012-304270

Choi, C.S. *et al.* (2016) The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. *Scientific Reports* 6, 36250 doi: 10.1038/srep36250

*INFACT also shared a paper on Fetal Valproate Syndrome prepared by Professor Jill Clayton-Smith and Dr Rebecca Bromley in March 2018. Please note however Dr Bromley, Professor Clayton-Smith,*

*Professor Turnpenny and Professor Wood have provided an up-to-date submission, please see Clinicians, academics and other individuals – Sodium Valproate.*

Committee for Safety of Medicines

Current Problems Sheet – January 1983 No. 9

This can be found in National Archives:

<https://webarchive.nationalarchives.gov.uk/20090218002312/http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2024512>



# Implications & Information Deficit For Sodium Valproate Prescribed in Pregnancy 1973 - 2014

The Independent Fetal Anti-Convulsant Trust (INFACT)



Independent Fetal Anti-Convulsant Trust (IN-FACT)

- **Background to IN-FACT.**

The Independent Fetal Anti-Convulsant Trust (IN-FACT) was re- launched in November 2012 to support and giving relief and assistance to all affected persons whose disabilities were caused by their mothers taking a medication known as, or used as an Anti-Convulsant Medication to treat their condition during pregnancy. Not all children who are exposed to anticonvulsant drugs are affected and the level of risk is determined by known factors such

as type of anticonvulsant and dose of anticonvulsant and unknown susceptibility factors. Children who are diagnosed with a Fetal Anticonvulsant Syndrome (FACS) are diagnosed by a medical specialist due to a constellation of physical and neurodevelopmental deficits they present with.

- **Prevalence of the problem.** It is estimated that around 0.5-1% of newborns may be exposed prenatally to an anticonvulsant drug. Sodium valproate reportedly carries the largest risk to developing infants and continues to be prescribed widely across a range of neurological and psychiatric conditions. According to prescription records (DINLINK data) there were over 21,500 women taking sodium valproate in 2010 in England and Wales. Scientific data demonstrates that around 10% of children exposed to sodium valproate will be born with a major congenital malformation (Samran et al 1997), their IQ is likely to be lower (Meador et al 2009), with 29% requiring additional educational support (Adab et al 2001) and with 6% being diagnosed with significant social-communication difficulties such as autism (Bromley et al 2008). With the latest research completed and published on 31<sup>st</sup> January 2013 (Bromley et al 2013) stating ‘ A 6 or 10 times increased prevalence of neurodevelopmental disorders is reported here for children with a history of prenatal VPA exposure respectively for monotherapy and polytherapy exposure....’ ‘The increase prevalence of ASD’s within this group is consistent with [previous retrospective clinical research and reports from animal studies’
- Many children will not have received a diagnosis of FACS, particularly if they do not have a major congenital malformation such as a heart defect or spina bifida, as they are less likely to be referred to a Clinical Geneticist. It is therefore very difficult to ascertain a figure pertaining to the number of children affected in the UK. Considering the percentage of impairment noted in the scientific literature and considering the timescale since anticonvulsants, and sodium valproate in particular, it is likely that there are thousands of children affected. At present the Fetal Anti-Convulsant Syndrome Association (FACSA) has over 700 families where approx. 1000 children have been affected by Sodium Valproate.
- **History of the problem and the development of scientific knowledge over time.** Throughout the 1960s, 1970s and 1980s a number of case reports were published in the medical and scientific literature which described children who had been exposed to one or more anticonvulsant drugs and had one or more major birth defects. These case reports

described children who had been born with a range of defects including spina bifida, cleft palate, heart defects and limb malformations. Some of the children in these case reports were also reported to have mental retardation, neurodevelopmental delay or a learning disability whilst others were too young for this to be known. Birth defects occur for a number of reasons and individual case reports are not enough to show that the malformation in that child was likely to have been caused by the exposure in the womb to the anticonvulsant. A number of case reports however reporting the same type of defect in the children indicate that closer investigation is required, with the latest research in 2013 showing cause for concern due to the growing numbers of children with Neurodevelopmental problems and diagnosed Autistic Spectrum Disorders where the mother has taken Valproate during the pregnancy.

- **Group studies: birth defects**

Investigations into groups of children who have been exposed to a particular type of anticonvulsant provide a more reliable insight into the risks associated with exposure. Early studies conducted in France and the UK demonstrated that there was a potential increased risk of birth defects to children exposed to anticonvulsant medications. In particular research in the 1970s and 1980s raised questions about the risks associated with phenobarbital (Luminal), phenytoin (Epanutin) and primidone (Mysoline) exposure. Following the onset of use of sodium valproate (Epilim) concerns were also raised about the potential association between exposure in the womb to sodium valproate (Epilim) and spina bifida as well as other malformations.

Research in the 1990s delineated differences between the anticonvulsants and the birth defects they were associated with. Older antiepileptic drugs such as phenytoin (Epanutin), phenobarbital (Luminal) and primidone (Mysoline) were noted to be associated with cleft palate and/ or lip and heart defects, whilst sodium valproate and, to a lesser extent, carbamazepine were noted to be associated with an increased risk of spina bifida. The largest

risk for having a child with a birth defect has been demonstrated to be associated with the use of sodium valproate (Epilim). As well as the type of anticonvulsant, the dose taken has also been demonstrated by research to be key to the level of risk conveyed to the developing foetus. For example, the risk of having a child with a malformation or experiencing learning disabilities is higher when the dose of sodium valproate is over 1000mg daily.

More recently large registers of pregnancies both nationally and internationally have increased our understanding about the level of risk with each of the anticonvulsants. The largest of these is the EURAP study whose recent publication studied 3909 of women with epilepsy and their children (Tomson et al 2011) This study found that in comparison to children exposed to low doses of lamotrigine (less than 300mg daily) a high doses of carbamazepine (Tegretol) (above 1000mg daily) was associated with an increase in risk of 4 times. High doses (greater than 1500mg daily) of sodium valproate (Epilim) were associated with an increase in risk of 16 times with high doses (greater than 150mg daily) of phenobarbital (Luminal) were associated with an 8 times increased risk. Lower doses of all three of these anticonvulsants were still associated with increased risks in comparison to lower dose lamotrigine but the risks were substantially smaller.

A key finding across all research published is that whatever the level of risk **not** every child is effected following prenatal exposure to anticonvulsants. Answering why some children are affected whilst others are not is complex and is likely to be linked to variations in exposure (e.g. amount that gets across the placenta), how the mother and/or the foetus metabolises the drug and the genetic makeup of the foetus.

- **Group studies: Neurodevelopmental Outcome/Learning Disability**

Exposure in the womb to anticonvulsant drugs has also been associated with an increased risk to the developing brain which leads to what historically was termed 'mental retardation'. This term has been replaced with the term 'learning disability' in the UK and refers to someone who experiences difficulties in acquiring knowledge and skills to the level expected for their age. More recently research has turned its attention to the cognitive (thinking) and behavioural abilities of children exposed to anticonvulsants in the womb.

Similar to the findings relating to birth defects the type and dose of an anticonvulsant are important when assessing the level of risk to the developing child. There is less research into this risk but our current level of knowledge suggests that exposure to sodium valproate

(Epilim) when the dose is above 1000mg daily carries the largest level of risk. Exposure at this level of sodium valproate (Epilim) has been reported to be associated with increased need for educational support and performance on IQ tests below the majority of their peers.

There is also evidence that children exposed to sodium valproate (Epilim) are at an increased risk of experiencing social-communication difficulties and are at an increased risk of being diagnosed with autistic spectrum disorders.

The evidence for carbamazepine (Tegretol) has been conflicting but, the majority of studies fail to find evidence that children exposed to carbamazepine (Tegretol) experience a higher incidence of learning disability. However, children who have been diagnosed with the physical symptoms associated with prenatal exposure and have a diagnosis of Fetal Carbamazepine Syndrome may be more likely to experience learning difficulties.

- **New Anti-Convulsants**

It takes a long time to collect data to investigate the longer term health and development of children exposed in the womb and therefore we are currently without adequate information about a number of antiepileptic drugs including:

levetiracetam, topiramate, zonisamide, lamotrigine, gabapentin

A small amount of research has been conducted which fails to find an association between levetiracetam or lamotrigine and reduced learning ability in children exposed in the womb, although this research mainly comes from a single research group and replication in other cohorts is required before conclusions can be made.

### **Sodium Valproate.**

The drug Sodium Valproate (Epilim) is manufactured by the pharmaceutical company Sanofi Aventis, amongst others, and has been prescribed in the UK since 1970s. Despite its efficaciousness for certain types of seizures, research has demonstrated that it carries a higher level of risk to the exposed foetus. The first case reporting the effects of Sodium Valproate during pregnancy appeared in 1981 and this grew to be a hot topic within the medical profession in the 1980's with numerous reports appearing in the Medical Journals. However, this was never investigated throughout the Review of Medicines between 1971 – 1990. The then Medicines Control Agency (MCA), which became the Medicines & Healthcare Regulatory Agency in 2004, did not pursue further the claims made by the medical research community. The MHRA Current Problems Reports touched

on the effects of Sodium Valproate from the No9 issue in 1981 and continued to do so intermittently as did the Current Problems papers issued by the Committee on Safety for Medicines from 1983. Still no action was taken to convince the pharmaceutical company, then Sanofi Synthelabo, to re-call the drug or improve it, or to provide comprehensive warnings to patients and their treating physicians..

From the early 90's the pharmaceutical company, which changed its name continuously during this time from Sanofi Pharma, Sanofi Winthrop and Sanofi Synthelabo becoming Sanofi Aventis in 2006, continuously insisted that the patient consulted the doctor for information when taking its drug during pregnancy, which is standard for a patient information leaflet. In 2005 Sanofi Aventis then added '*Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support*'.to its Patient Information Leaflets. Adding "*Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal or have autistic disorders.*" in 2011.

It is clear that both the Government and the pharmaceutical companies could have done more and taken further action to protect the public. It was the duty of Sanofi to keep up to date with known medical knowledge and to develop further research to ensure safety, passing this onto patients via the Patient Information Leaflet. It was the duty of the MHRA to ensure Sanofi investigated the medical research claims of birth defects caused by their products.

The delay in the establishment of research to investigate early scientific warnings and the failure to develop adequate preconceptual care for women requiring treatment with anticonvulsants during their child bearing years means that thousands of women have entered into pregnancy without being comprehensively informed about the level of risk, reducing their chances to make decisions about what treatment and at what dose.

Due to these delays it is our belief that thousands of children have been affected by exposure in the womb. It is our belief that due to the lifelong nature of the deficits experienced by children and adults with Fetal Valproate Syndrome that responsibility must be taken for these delays by both the Government and Sanofi Aventis.

# Appendix 1

## Time line: Key publications which altered the way we think about anticonvulsant exposure.

**1963** – Lawrence, A. Anti-epileptic drugs and the foetus. *British Medical Journal* 1973; 16; p267. Possibly the first report of problems in a child where an antiepileptic drug is considered the cause.

**1970** - Meadow, R. Congenital abnormalities and anticonvulsant drugs. *Proceedings of the Royal Society of Medicine* 1970; 63: p12-13. The first group study into the incidence of major malformations.

**1973** – Fedrick, J. Epilepsy and Pregnancy: a report from the Oxford record linkage study. *British Medical Journal* 1973; 2:p442-448. The first population based study.

**1974** – Hill, R et al. Infants Exposed In Utero to Antiepileptic Drugs: A Prospective Study. The first prospective study to investigate this issue.

**1974**- Barr, M., et al. Digital hypoplasia and anticonvulsants during gestation: a teratogenic syndrome. *The Journal of Pediatrics* 1974; 84(2):p254-256. The authors suggest that a syndrome may be associated with prenatal exposure to phenytoin, phenobarbital and primidone exposure.

**1975**- Hanson, J.W. & Smith, D.W. The fetal hydantoin syndrome. *The Journal of Pediatrics* 1978; 307: p285-290. Termed the constellation of features noted in some children following exposure to phenytoin, phenobarbital and primidone as *Fetal Hydantion Syndrome*.

**1976**- Hanson, J.W., et al. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis of the fetal hydantion syndrome. *The Journal of Pediatrics* 1976; 89(4): p662-668. The first paper to raise that a child's intellectual abilities may be lower in children with fetal hydantion syndrome.

**1980**- Dalens, B. Teratogenicity of valproic acid. *The Journal of Pediatrics* 1980; 97(2):p332-333. The first report of an infant with major congenital malformations thought to be linked to exposure to sodium valproate.

**1982** –Rovet, E. & Guibaud, P. Maternal valproic acid and congenital neural tube defects. *The Lancet* 1982; 2(8304): p937. – Demonstrates the potential association between prenatal exposure to VPA and spina bifida.

**1988** –Ardinger, H., et al Verification of the Fetal Anticonvulsant Syndrome. *American Journal of Medical Genetics* 1988; 29:p171-185– the first group case series of children exposed prenatally to sodium valproate and highlights potential characteristics of the syndrome.

**1996** – King, P.B., et al. Spina bifida and cleft lip among newborns of Norwegian Women. *American Journal of Public Health* 1996; 86(10):p1454-1457. Demonstrated that changes in anticonvulsant use across the country lead to an alteration in the type of birth defects seen in the children.

**1997** – Samren, E.B., 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; 38(9): p981-990. This collaboration of a number of different research groups highlights the importance of the dose of the drug.

**2000-** Moore, S., et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *Journal of Medical Genetics* 2000;37:p489-497. The first study into a group of children diagnosed with fetal anticonvulsant syndromes.

**2001** –Adab, N., et al. The longer term outcome of children born to mothers with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry* 2004; 75:p1575-1583. The first study to include a large group of children exposed to sodium valproate and to find that they require increased levels of educational support.

**2004-** Gaily, E., et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004; 62:p28-32. This large and well designed study found that the IQ of children exposed to carbamazepine was not significantly different from a group of un-exposed children.

**2006-**Hunt, S., et al. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; 67: p1876-1879. The first investigation into prenatal exposure to levetiracetam (Keppra) and birth defects.

**2008** –Hunt, S., et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008; 71: p272-276. The first paper to investigate prenatal exposure to topiramate.

**2008** – Bromley, R., et al. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008; 71: p1923-1924. The first prospective study to demonstrate an increased prevalence of autistic spectrum disorders in children exposed to sodium valproate.

**2009-** Meador, M., et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *The New England Journal of Medicine* 2009; 360(16): p1597-1605. The largest prospective study into sodium valproate and lamotrigine demonstrating that the first is associated with reduced IQ.

**2011** –Shallcross, R., et al. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 76; p383-389. The first study to investigate the rate of developmental delay in a group of children exposed to levetiracetam.

**2011-** Tomson, T., et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurology* 2011; 10: p609-617. The largest study to date which shows level of risk by dose of antiepileptic drug.

**2013** – Bromley,R.L., et al. The Prevalance of Neurodevelopmental Disorders in Children Prenatally Exposed to Antiepileptic Drugs. *Journal of Neurology, Neurosurg, Psychiatry*. 21013; **0**: 1-7.

*The information on this page is provided by Dr Rebecca Bromley, Clinical Psychologist and Researcher at the University of Liverpool.*

Approximation Figures for FVS from 1996

These figures have been calculated using the Summary of Live Birth Statistics from the Office of National Statistics (ONS) for England and Wales from 1996 – 2011 and the Man *et al* paper 'Antiepileptic Drugs during Pregnancy in Primary Care: A UK Population Based Study' (2012)

The figures from the documents together show the year, number of births for each year and the percentage of pregnancies where Valproate was taken. The calculations show that:

<u>Year</u>	<u>ONS Births in this year</u>	<u>% of births where Valproate taken</u>	<u>No. of babies exposed to Valproate</u>
1996	649,485	0.1%	649
1997	643,095	0.25%	1607
1998	635,901	0.2%	1271
1999	621,872	0.2%	1243
2000	604,441	0.2%	1208
2001	594,634	0.1%	594
2002	596,122	0.15%	894
2003	621,469	0.1%	621
2004	639,721	0.1%	639
2005	645,835	0.1%	645
2006	669,531	0.05%	334
2007	690,013	0.1%	690
2008	708,711	0.1%	708
2009	706,284	0.1%	706
2010	723,913	0.1%	723
2011	723,165	0.1%	723

Therefore between 1996 – 2011 the approximate number of babies born to women taking Sodium Valproate is **12,047**.

***It has been noted that approx 40% of those exposed to Valproate in pregnancy will have significant cognitive and/or physical disabilities. (Meador et al, 2013)***

***Scientific data demonstrates that 10% of children exposed to Valproate in pregnancy will be born with a major congenital malformation (Samran et al, 1997)***

Applying these figures **4,818** of the **12,047** exposed children between 1996 – 2011 are likely to have been significantly affected in some way with Neurodevelopmental problems, reduced life changes, long term employment and care issues, and a health/educational/social care burden on the state. Bearing in mind that Valproate has been licenced since 1973, the actual overall number of those exposed in the UK could be as high as 33,798 of which between **13,510- 20,000** may have been significantly affected.

#### Cost Calculations of Valproate

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- Using the APPG for Autism calculations from 2001 ‘Impact of Autism’ Fiona Loynes June 2001:

**“In the UK the average lifetime cost per person with Autism is £2,940,538”**

- Using the figures from this paper calculated for each individual resource required by a child affected by Autism, and taking into consideration that the majority of children affected by Valproate taken in Pregnancy also has a diagnosis of an Autistic Spectrum Disorder, our figures for cost per annum are as below:

### Health Care Costs Per Person Per Annum:

	£
GP's appointments (3 per month, 36 per annum)	900.00
A & E visits (1 per year)	117.00
Walking Centre Visits (3 per months, 36 per annum)	2268.00
Cost of Autism treatment per annum	58,810.00
Prescriptions on average (4 items)	367.00
Clinical Psychology (Anxiety etc..) 8 sessions	472.00
SALT 8 sessions	296.00
Occupational Therapy 8 sessions	1568.00
Physiotherapy 8 sessions	1576.00
Mental Health services	480.00
Adaptations/Special Equipment	1000.00
Home Adaptations	30,000.00
Social Worker	29,378.00
Play schemes School Hols	1,900.00
Residential School	30,000.00
Tribunal Process	2,300.00
Home Programme Early Intervention	20,000.00
FE College Support	21,000.00
TOTAL	£202,432.00

### DWP Costs

DLA (Middle Care, Low Mobility)	3600.00
ESA	6760.00
Carers Allowance	3094.00
Housing Benefit	6760.00
Council Tax Benefit	1800.00
Income Support (For Carer)	2652.00
TOTAL	£24,198.00

### Cost Calculations Over Time

Health/Education Cost	£202,432.00
DWP Costs	£24,198.00
GRAND TOTAL (Per Annum)	£226,630.00

### Up to Childs 18<sup>TH</sup> Birthday

£226,630.00 x 18 = £4,079,340 . 00

### Costs over 40yrs Valproate on Market (1973)

£226,630.00 x 40 = £9,065,200 . 00

Considering approx. 20,000 children affected by Valproate (Figures agreed with the MHRA 1<sup>6TH</sup> August 2013)

£9,065,200 . 00 x 20,000 = £181,304,000,000 . 00

### APPENDIX - References:

The Impact of Autism: A report compiled for the APPG on Autism  
By Fiona Loynes 2001

NHS Feeling Unwell: Get the right treatment and help the NHS manage its resources. 2013

NHS Choices: Parent Caring, Aids & Adaptations  
[www.nhs.uk/carersDirect](http://www.nhs.uk/carersDirect) 2013

### Progression Outline of Valproate

#### Progression Outline of Information

ABPI = 1979 (Assoc of the British Pharmaceutical Industry)  
BNF = 1991 (British Medical Association (BMA))  
PIL = 1996 (Sanofi)  
SPC = 1996 (Sanofi)

#### ABPI datasheets stated:

Teratogenicity in animals in 1979-80

#### BNF stated:

Increased risk of Neural Tube Defects in 1991

#### Sanofi published:

PIL's & SPC's in 1996 stating:

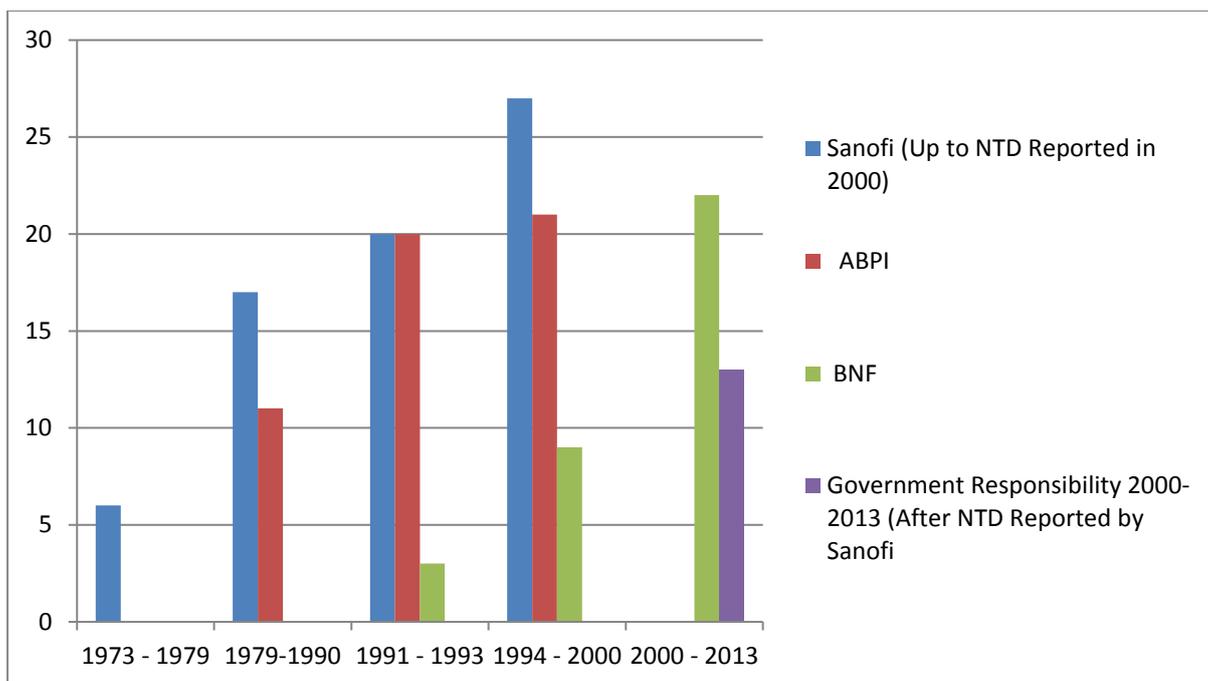
'IF PREGNANT PLEASE CONSULT YOUR DOCTOR'

With no mention of Neural Tube Defects (Spina Bifida) to the patient until 2000.

#### NICE Guidelines stated in 2004:

*'In order to enable informed decisions and choice, and to reduce misunderstandings, women & 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 the menopause.'*

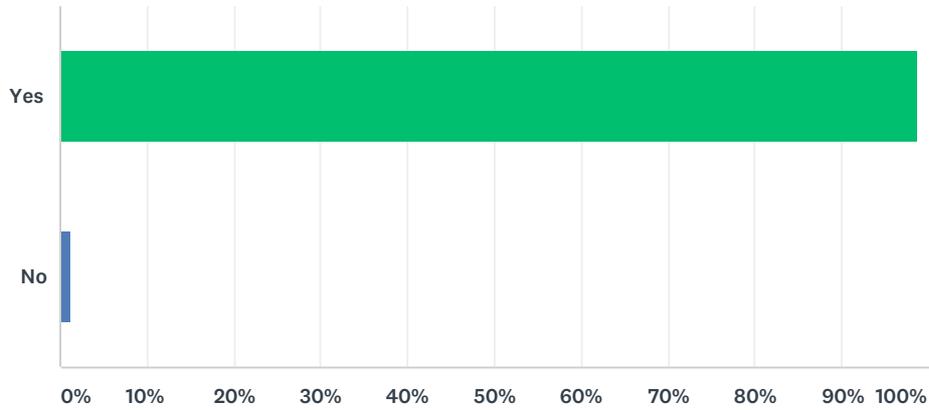
Number of Years



*INFACT also shared a paper on Fetal Valproate Syndrome prepared by Professor Jill Clayton-Smith and Dr Rebecca Bromley in March 2018. Please note however Dr Bramley, Professor Clayton-Smith, Professor Turnpenny and Professor Wood have provided an up-to-date submission, please see Clinicians, academics and other individuals – Sodium Valproate.*

### Q1 Have you been prescribed any form of Sodium Valproate over the past 2 years and continue to do so.

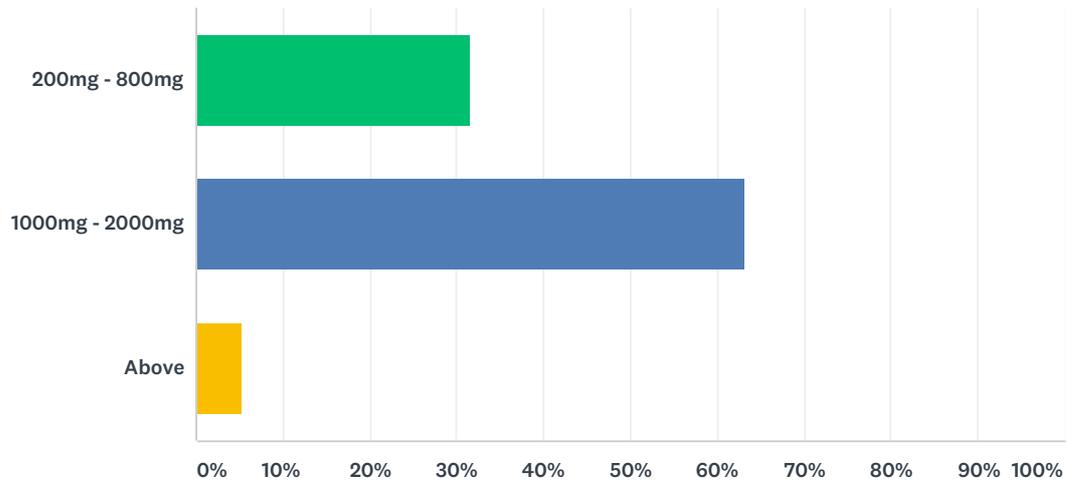
Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	98.70%	76
No	1.30%	1
TOTAL		77

## Q2 What is your dose of Valproate per day

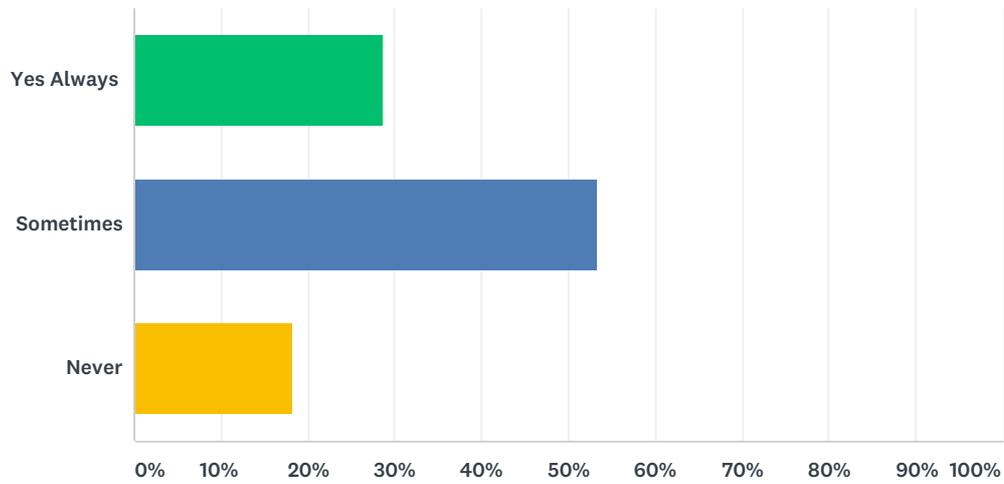
Answered: 76 Skipped: 1



ANSWER CHOICES	RESPONSES	
200mg - 800mg	31.58%	24
1000mg - 2000mg	63.16%	48
Above	5.26%	4
<b>TOTAL</b>		<b>76</b>

### Q3 On collection of your prescription from the Pharmacy, do you receive your tablets/medicine in a Purple Box

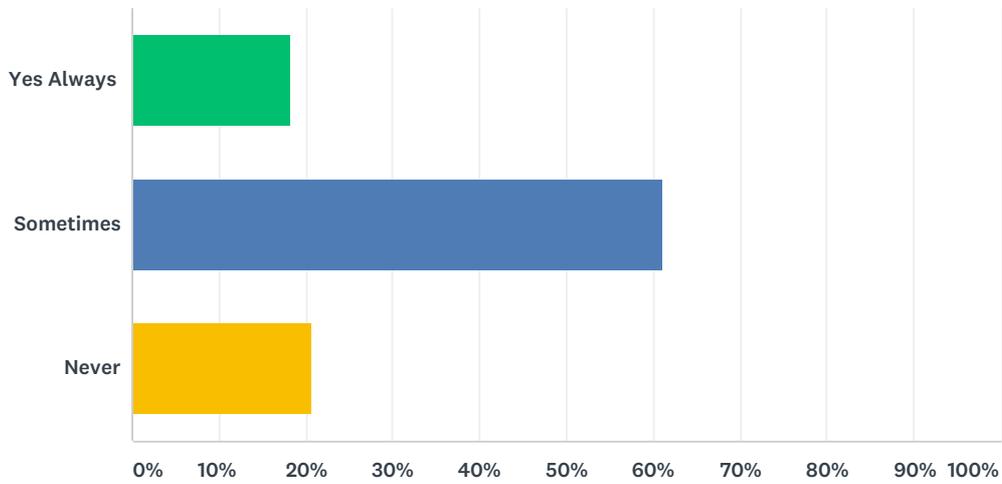
Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes Always	28.57%	22
Sometimes	53.25%	41
Never	18.18%	14
TOTAL		77

### Q4 Or, on collection of your prescription from the pharmacy do you receive your medication in a White Chemist Box

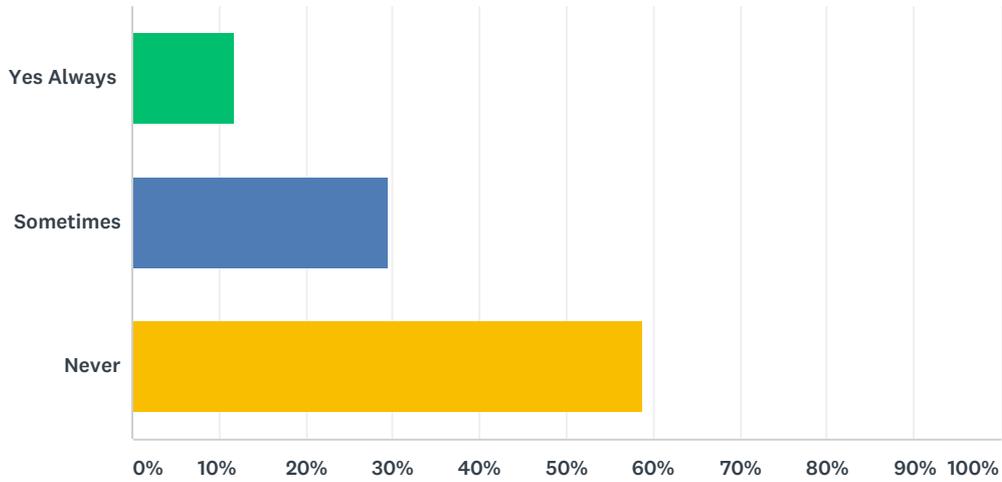
Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes Always	18.18%	14
Sometimes	61.04%	47
Never	20.78%	16
TOTAL		77

### Q5 If you receive the White Chemist Box, does it contain a Patient Information Leaflet

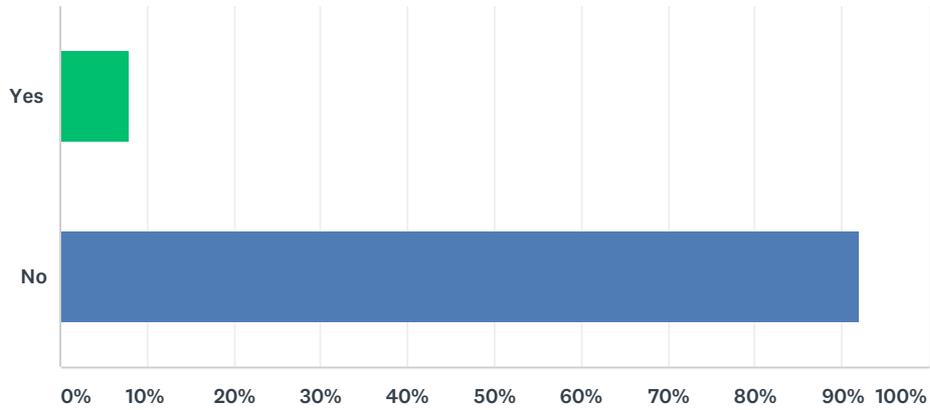
Answered: 68 Skipped: 9



ANSWER CHOICES	RESPONSES	
Yes Always	11.76%	8
Sometimes	29.41%	20
Never	58.82%	40
TOTAL		68

### Q6 Have you received a small credit card size information from your pharmacist

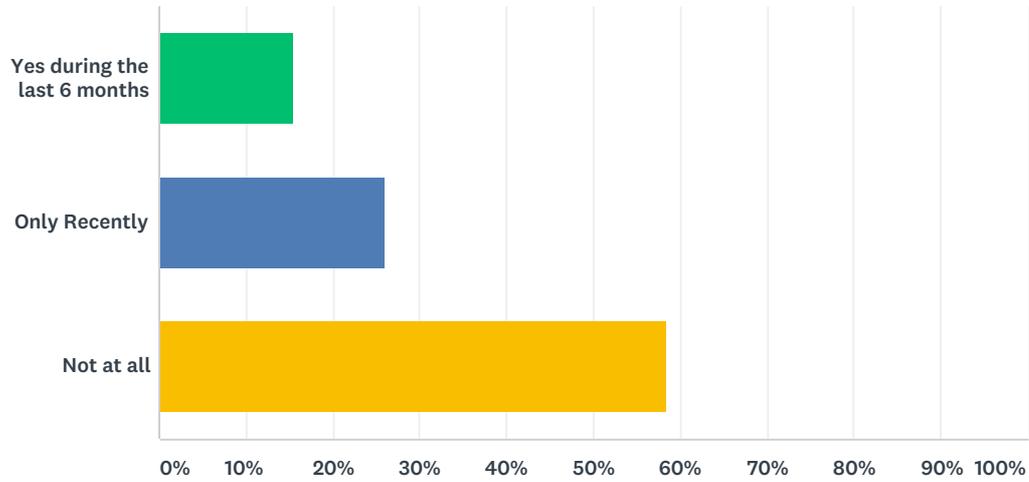
Answered: 76 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	7.89%	6
No	92.11%	70
TOTAL		76

## Q7 Over the past 6 months, has your GP discussed with you the New Warnings on Valproate in Pregnancy

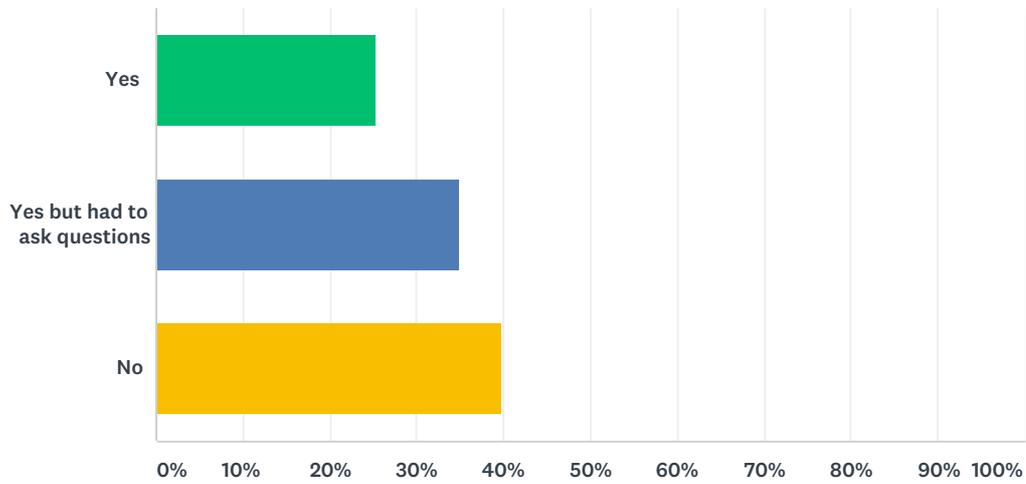
Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes during the last 6 months	15.58%	12
Only Recently	25.97%	20
Not at all	58.44%	45
TOTAL		77

### Q8 If you have discussed with your GP or Neurologist, was it done in a way your fully understood

Answered: 63 Skipped: 14



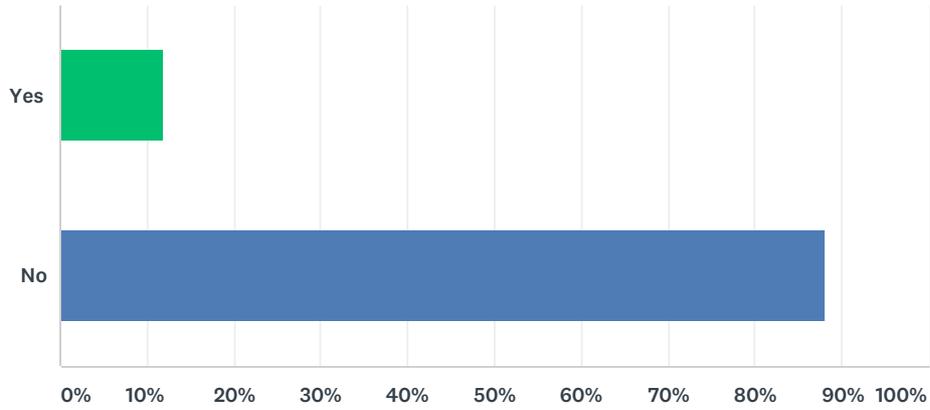
ANSWER CHOICES	RESPONSES	
Yes	25.40%	16
Yes but had to ask questions	34.92%	22
No	39.68%	25
TOTAL		63

**Q9 If your answer to number 8 is No, please explain why you did not understand fully.**

Answered: 23 Skipped: 54

### Q10 Have you been asked to sign an Acknowledgment of Risk From by your GP/Neurologist to say you have been told of the risks of Valproate in pregnancy

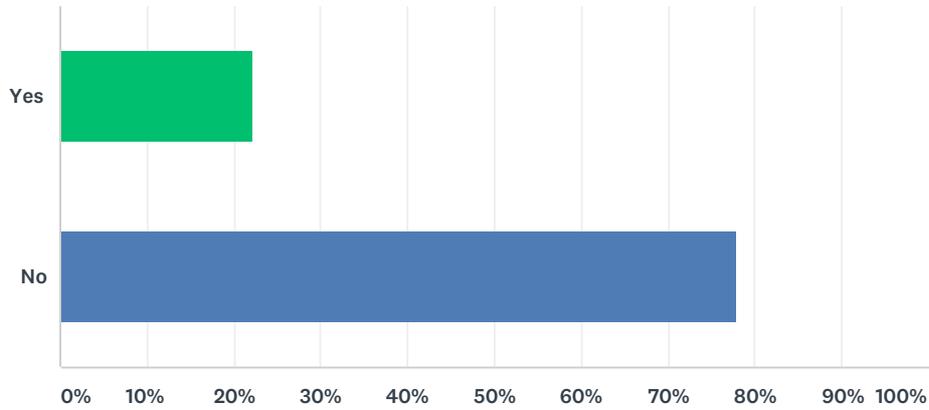
Answered: 75 Skipped: 2



ANSWER CHOICES	RESPONSES	
Yes	12.00%	9
No	88.00%	66
TOTAL		75

### Q11 Has your GP, Neurologist or Psychiatrist suggested a change in medication, other than Valproate

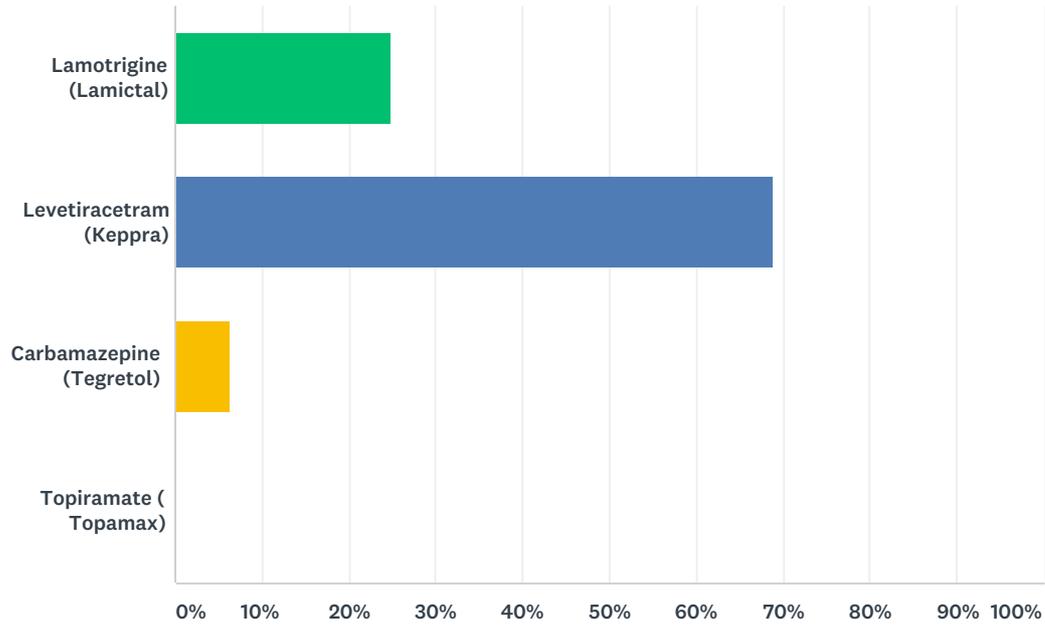
Answered: 77 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	22.08%	17
No	77.92%	60
TOTAL		77

## Q12 Which medication for Epilepsy has he/she suggested your try

Answered: 16 Skipped: 61



ANSWER CHOICES	RESPONSES	
Lamotrigine (Lamictal)	25.00%	4
Levetiracetam (Keppra)	68.75%	11
Carbamazepine (Tegretol)	6.25%	1
Topiramate ( Topamax)	0.00%	0
<b>TOTAL</b>		<b>16</b>

**Q13 If you are prescribed Valproate for any other condition such as Bipolar or Migraine please note which medication, other than Valproate your Dr has suggested for you.**

Answered: 18 Skipped: 59

**Q14 Thank you for taking the INFACT Survey on Valproate - Pregnancy Prevention Information, if you have children already affected by Valproate in pregnancy who are born in the UK and wish your names to be added to the INFACT Database please add your details below.**

Answered: 40 Skipped: 37

ANSWER CHOICES	RESPONSES	
Name	100.00%	40
Company	0.00%	0
Address	95.00%	38
Address 2	60.00%	24
City/Town	85.00%	34
State/Province	0.00%	0
ZIP/Postal Code	95.00%	38
Country	0.00%	0
Email Address	97.50%	39
Phone Number	95.00%	38

Q15 If you have completed the contact form these 2 questions are important:  
A) Does your child/children have a diagnosis of Fetal Valproate Syndrome  
B) What was your dose of Valproate during pregnancy

Answered: 49 Skipped: 28

**Q16 If you have any questions or need further information on Fetal Valproate Syndrome or Valproate in Pregnancy please visit our website at <https://infactuk.com/>**

Answered: 5 Skipped: 72



**IMMD**  
**Valproate Review**  
**CALL FOR EVIDENCE**

2<sup>nd</sup> Submission

INFACTs evidence relates to the avoidable harm caused by the prescribing of Sodium Valproate (Epilim) in pregnancy from the date of licence in 1972/3, and before.

Our evidence touches upon the fact that the irreversible damage caused by Valproate on the fetus, and the purposeful avoidance by governing bodies of information to women of child bearing age, while holding the knowledge of the dangers of earlier anticonvulsants in pregnancy.

Valproate's dangers were known to the Committee of Safety of Medicines, the Committee for safety of Drugs, and sub committees for toxicology, teratology and adverse reactions, yet continuously for 45 years the damage caused to babies has been hidden from view of the public and patients prescribed it.

INFACT feel it is necessary to uncover documents which may have never been seen before and have been hidden in the archive away from the eyes of the public for so long, giving those prescribed Valproate and other AED's in Pregnancy the opportunity to plan and be informed of the risks.

Independent Fetal Anti-Convulsant Trust (INFACT)

Valproate – Medicines & Medical Devices Review

November 2018

Key Points

From May 1971 – 2018

- 1) Refer to Document 1 - Committee on Safety of Drugs/Adverse Reactions – 19<sup>th</sup> May 1971 (1st paragraph) shows concern for Anti-convulsant drugs in pregnancy had begun before the licencing of Valproate in 1972.
- 2) Refer to Document 2 – Product Licence application for Valproic Acid/Labazene (Depakine/Depakene) Dated 7<sup>th</sup> September 1971. **(Please note Product Licence Number – PL/0623/1000**
- 3) Refer to Document 3 – PL/0623/1000 – Labazene. Sub Committee on Toxicity & Clinical Trials (January 1972). Product was deferred pending discussion. May 1972 – Product Licence refused due to inadequate information on Toxicology and Teratology.
- 4) Refer to Document 4 – PL/0623/1000 – Labazene Tablets. Recommendation stated: Satisfactory for Marketing.
- 5) Refer to Document 5 – “Dosing regimes for investigation of drug effects on fetus & Neonate” 1972.  
Quote: ***“It may also be felt that it would be undesirable for the committee to lay down detailed and rigid procedures for the investigation of drug effects on the fetus and neonate”***
- 6) Refer to Document 6 – Minutes of a meeting, Committee on Safety of medicines (Sub Committee for Adverse Reactions) 18<sup>th</sup> July 1973.  
Quote: ***“Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that by ICI could be included in all relevant datasheets but not on packaging inserts so that there would be no danger of patients themselves seeing it”***
- 7) Refer to Document 7 – Change in recommendations on Valproate in March 1974 noted the compound  
Quote: ***“... has been shown to be teratogenic..”***  
New recommendations noted:  
***“For use in generalised, focal or other epilepsy. In women of child bearing age, it should only be used in severe cases or those resistant to other treatments.”***

This recommendation was released again in 2015 by the Medicines and HEALTHCARE Products Regulatory Agency (MHRA) as a new instruction in the Valproate Toolkit, which went on to fail.

Previous to the Valproate toolkit, prescribers had been using Valproate as the first treatment to try in women with Epilepsy, against the recommendations of the CSM noted on the Data Sheet in 1974.

8) Refer to Document 8 – Data Sheet released for Epilim – Product number PL/0623/0001 June 1974. Following recommendations as above it was noted ***“Precautions – Women of child bearing age. In animals, this compound has demonstrated teratogenic properties in laboratory experiments. Any benefit from its use should be weighed against the possible hazard suggested by this finding”***

9) ABPI – Data sheet Compendium 1979-1980

10)

Epilim – ***“Women of child bearing age – Sodium Valproate, like certain other anticonvulsants has been shown to be teratogenic in animals. In women of child bearing age the benefits of these compounds should be weighed against the possible hazard suggested by these findings”***

With a slight mention of other anticonvulsants implies that Valproate has a greater effect on the fetus.

#### Patient Information Leaflets:

11) A. 1995

B. 1996 - Both these leaflets stated ***“If you are likely to become pregnant tell your Doctor”***

C. 2001 - Noted possible Spina Bifida and the need for folate.

D. 2005 - Noted some babies born to Epilim may develop less quickly and require Educational support.

E. 2006/7 - Extended information with little urgency to avoid pregnancy

It is important to note that the majority of women prescribed Valproate did not receive a Patient Information Leaflet with their dispensed medication, and that, still up to 2018 prescribed failed to pre warn women of the danger of valproate (Epilim/Depakote) in pregnancy.

NOT FOR PUBLICATION

93D(AR)(71)17

Committee on Safety of Drugs

SUB-COMMITTEE ON ADVERSE REACTIONS

Monitoring of Congenital Abnormalities

19 MAY 1971

Introduction

It is likely that, during the seven-year period in which reports of adverse reactions have been collected by the Committee on Safety of Drugs, at least 200,000 babies with congenital defects have been born many of them, presumably, to mothers who have been treated with drugs during pregnancy, and it must therefore be a matter for some concern that only 300 to 350 reports of congenital abnormalities have been received during this same period. It has been recognised for a long time that the early-warning system, based on voluntary reporting of suspected adverse reactions, is insufficiently sensitive to enable the Committee to identify the possible teratogenic hazards of drugs used during human pregnancy.

Because of multiple drug and reaction coding, it is not possible, by examination of current printout to arrive at an accurate figure for the total number of reported congenital abnormalities, the figure of 300 to 350 is only an estimate of the number of reports that have yielded the total of 858 combinations of drug and deformity that are summarised in table I. There is considerable overlap due to multiple-drug prescribing. For example, the rather large number of cases of cleft-palate linked with the barbiturates are mostly the result of the addition of phenobarbitone to other anticonvulsant therapy. Similarly the 25 reported associations between vitamins and limb deformities are mainly due to the inclusion of pyridoxine in antihistamine preparations. Although there may be an association

25.

1

between cleft-palate and the use of certain anti-convulsant drugs, no other important problem has been demonstrated by the small number of reports of abnormalities have been received. Since probably the majority of women use one or more drugs (either prescribed or "handbag") during early pregnancy, it seems extremely unlikely that the current input of voluntary reports will enable the Committee to detect human teratogens reliably. Perhaps the most important reason for the small number of reports is the long time interval between the maternal exposure to a drug and the recognition of an abnormality.

Epidemiological Studies

The drug-histories of many thousands of women would have to be ascertained in any prospective study in order to identify a population of patients exposed to any one agent, for significant associations between that agent and abnormal births

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to be revealed. Prospective studies are likely to be time consuming and extremely expensive. For this reason, in 1969, a pilot study was set up by the Sub-Committee in order to assess the feasibility of retrospective surveys by the Committee's team of medically qualified field workers. The results of this pilot study are described in the appendix to this paper. Abnormal births were identified by the Registrar General and the field workers established the identity of the mother's doctor through the local Medical Officers of Health. 117 abnormal babies were identified and the field officers succeeded in interviewing 87 doctors and obtaining maternal drug-histories and control data. Data relating to the drug-history of the mothers was divided into two classes. Class 1 included records made by the doctor before the delivery of the abnormal baby and Class 2 data which he may have added to the record after the birth. Only Class 1 data were considered in the analysis.

The mothers of babies with deformities were recorded as having used more drugs than control mothers, but no significant association with any one agent was detected in these small numbers of patients. A most unexpected finding was that there was a positive history of drug use in 11 of 23 mothers of babies with hare-lip or cleft-palate, while none of the control mothers gave a positive history. No explanation for this has been found.

This exercise demonstrated that a retrospective screening technique was practicable and also that the quality of most general practitioners' records was much higher than anticipated. The procedure was inexpensive and the analysis

500 to 1,000 similar investigations each would be well within the capabilities of the medical officers currently available for field work and the Committee may feel that this would provide a useful screening procedure for the detection of teratogens. In a sense it could be regarded as an extension of the early warning system and it is even possible that, once a potential hazard had been identified, the same technique might be employed for further "in depth" studies of a specific problem.

NO OTHER

Document 2 – Labazene Application

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No. PL/0623/0001

Date received 7th Sept. 1971

Meeting January

Previously considered -

Therapeutic class Anti-convulsant

- 1 -

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COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON TOXICITY, CLINICAL TRIALS AND THERAPEUTIC EFFICACY

MEDICINES ACT 1968 - APPLICATION FOR A PRODUCT LICENCE.

SUMMARY AND REPORT

1. LICENCE TO BE HELD BY: Pharmacy Products U.K. Ltd., London, W.1.

2. PERIOD OF VALIDITY: 5 years.

3. NAME UNDER WHICH THE PRODUCT IS TO BE MARKETED: Labazene Tablets.

4. DESCRIPTION AND COMPOSITION OF DOSAGE FORM: Uncoated tablets containing Sodium dipropyl acetate 200mg.

5. MANUFACTURER: Sapchim-Fournier-Cimag, Paris.  
5.1. of drug substance: Arthur H. Cox, Brighton

6. CHEMISTRY AND PHARMACOLOGY:

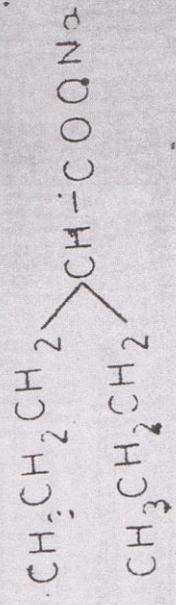
6.1. Active Ingredient - Chemical Identity

Names -	(i)	Approved Name	Valproic Acid (Sodium Salt)
	(ii)	INN/USAN	None
	(iii)	Laboratory Code	S2411N
	(iv)	Chemical Name	Sodium DPA
	(v)	Alternative Chemical Names	Sodium Dipropylacetate
			Sodium propyl-2-pentanoate
			Sodium propyl-2 valerionate
	(vi)	Proprietary Name	Labazene
	(vii)	Other Names	Depakine, Eurekene, Depakene.

Description

A hygroscopic, white, microcrystalline powder.

Structural Formula



6.2. Dosage Form complete formula

mg/tab  
200

Active constituent

Sodium Dipropyl acetate

Other constituents

Starch BP

Kaolin BP

Magnesium Stearate BP

Colloidal Silicone Dioxide USNF

(Vol, 1, P. 112)

150  
20  
10  
20

7. RECOMMENDED CLINICAL USE (Vol, 1, P. 112)

- 1) Generalised epilepsy (petit mal, grand mal, mixed epilepsy).
- 2) Focal epilepsy (psychomotor epilepsy).
- 3) Other epilepsy (myoclonic, akinetic).

8. RECOMMEND DOSAGE (Vol 1, P. 112)

Adults 1000-1400mg/day (divided doses b.d. or t.d.s.)

Children

20-30mg/kg (/day); minimal dose 400mg/day irrespective of age (divided doses b.d. or t.d.s.).

Valproic acid may be given with all other anti-epileptic drugs. With previous medication, valproic acid is initiated at a dose in about 10 days. The previous

9. SIDE-EFFECTS (Vol 1, p.112)

Some patients have gastro-intestinal symptoms at beginning of treatment (nausea, "gastralgia", controlled by metoclopramide).

PRECAUTIONS AND CONTRA-INDICATIONS (Vol 1, p.112)

1) Valproic acid potentiates phenobarbitone, the dosage of which should be reduced.

The dosage of other neuroleptic drugs should also be reduced.

2) Valproic acid is not indicated in "BJ epilepsy" (Bravais-Jacksonian) or

3) Valproic acid must not be administered with "carbonated" or alcoholic drinks.

(NB. The draft technical booklet warns that valproic acid causes false positives in tests for urinary ketones).

11. PHARMACODYNAMICS (Vol 1)

A. Swinyard (pp. 119-167)

(i) Anti-convulsant activity

a) Time to Peak Effects (pp. 121-124)  
Using MES, valproic acid (500-600mg/kg) orally in rats and mice

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gave peak effect in 1-1 hour c.f. 3 hours with phenobarbitone (6-35mg/kg) and phenytoin (15-40mg/kg). After i.v. administration, peak effect of valproic acid occurred at 1-1/2 hour c.f. approximately 2 hours for phenobarbitone.

Judged from toxic effects, time to peak effect i.p. in rabbits and rats was 1/2 hour.

(NB. Concluded that valproic acid has "more rapid onset of action than clinically established anti-convulsants" but effects were also generally of much shorter duration.)

b) Comparative Anti-Convulsant Activity (pp. 126-134)

Assessed by MES, anti-Metrazol and minimal electroshock seizure threshold in mice and rats. Therapeutic ratios calculated from ataxia-producing dose and anti-convulsant ED50. Valproic acid was generally less potent than phenobarbitone, phenacemide and phenytoin and more potent than troxidone; therapeutic ratio was less than with phenacemide and phenobarbitone but marginally better than troxidone and phenytoin.

Valproic acid was active against MES and Metrazol in cats and rabbits but therapeutic ratios were poor (0.3-1.6).

c) Other Anti-Convulsant Activity (pp. 135-136)

therapeutic ratios of 1:1.7

ii) Other CNS Actions

a) Righting Reflex in Mice (pp. 135-137)  
Less sedative than phenobarbitone but more sedative than troxidone or phenacemide.

b) Hexobarbitone Sleeping Time in Mice (pp. 135-139)  
Equivalent fractions of the ataxia-producing dose prolonged hexobarbitone sleeping time more than phenobarbitone, phenacemide or troxidone, but less than pherytoin.

c) Tranquillising Activity (pp. 138-141)  
No significant activity in ataxia-producing doses (amphetamine toxicity in aggregated mice; conditioned avoidance in rats).

d) Analgesic Activity (pp. 138-141)  
Valproic acid, phenobarbitone and troxidone in ataxia-producing doses had no effect on rat tail flick whereas codeine was significantly analgesic.

e) Anti-pyretic Activity (pp. 144-147)  
No effect on normal body temperature in mice and rats; inactive against yeast-induced hyperthermia in rats.

f) Spontaneous Motor Activity (p. 148)  
No significant effect.

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111) Autonomic and Cardiovascular (pp. 148-151)

In anaesthetised cats, 25-100mg/kg valproic acid i.v. reduced blood pressure, not modified by autonomic blocking agents. No significant changes in heart rate, ECG, respiration or nictitating membrane.

iv) Other Pharmacological Properties

a) Anti-Histamine (pp. 151-153)

Inactive against histamine-induced asthma and egg white anaphylactic shock in guinea-pigs.

b) Renal Effects (pp. 153-156)

No significant diuretic or anti-diuretic effect.

c) Smooth Muscle (pp. 153, 157-158)

Spasmolytic action on rat ileum at  $2 \times 10^{-3}$  g/ml.

d) Coagulation and Prothrombin Times (p. 157)

Inactive at maximal anti-convulsant doses.

f) Oxygen Consumption (p. 159)

Some reduction with ataxia-producing doses.

B) C. Carraz (pp. 169-209)

Results in routine laboratory tests broadly similar to those described in previous report.

ECOG recordings in rats showed pronounced antagonism of Metrazol-induced voltage changes (pp. 180-181)

Doses of generally 200mg/kg valproic acid i.p. were without anti-convulsant activity against strychnine, picrotoxin, thuyone or cocaine (pp. 185-189).

Combination of low doses of phenobarbitone and valproic acid had increased anti-convulsant effect (pp. 189-190)

Judged from abolition of righting reflex, mainly in mice, valproic acid gave slight potentiation of phenobarbitone, hexobarbitone, mebubarbital and thiopentone and pronounced potentiation of pentobarbitone, chloral and ether (pp. 191-199).

C) Mennier et al, Lebreton et al (pp. 211-231)

Virtually complete duplication of above report by Carraz.

D) Eymard and Mestre (pp. 409-418)

Wistar male rats dosed i.g. for 111 days with increasing doses of

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c) Elimination

Blood levels maximal at 30 minutes, almost absent by 24 hours.

Urinary excretion evident at 5 minutes; approximately 70% of administered dose excreted by 24 hours.

Approximately 2% of dose excreted as CO<sub>2</sub> in 24 hours; less than 3% in faeces.

Biliary radioactivity maximal at 1 hour, falling rapidly until 4 hours when approximately 7% of administered dose had been excreted. Enterohepatic circulation demonstrated by donor-recipient experiments. Radiochromatograms of bile showed spots corresponding to unchanged valproic acid and 6 unidentified metabolites.

d) Placental Passage

5-10µC/animal on day 15 of gestation in rats and day 10 in mice.

Autoradiography and scintillation counting showed negligible amounts of drug in foetus and only low concentrations in placenta.

iii) Simler et al (p. 251)

changing levels of aspartic or glutamic acids, glutamine or glycine.

Raised GABA levels not due to increased formation but may be related to in vitro inhibition of GABA-T.

v) Bernard (pp. 260-279)

In rabbits on high cholesterol diet, 250mg/kg i.v. valproic acid for 40 and 60 days claimed unconvincingly to lower blood cholesterol levels but on return to normal diet blood levels definitely returned to normal more rapidly than in untreated animals. 125 and 250mg/kg i.v. valproic acid reduced fatty infiltration of liver macroscopically and microscopically.

Judged from BSP excretion, 250mg/kg valproic acid (like betaine) protects guinea-pigs against hepatotoxic effect of CCl<sub>4</sub>.

The data is used to evidence lack of hepatotoxicity of therapeutic doses of valproic acid.

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16. SINGLE DOSE TOXICITY STUDIES

Vol 1, pp. 123-126, 234-241.

<u>Species</u>	<u>**Animals/ Group</u>	<u>Route</u>	<u>Duration (Days)</u>	<u>LD<sub>50</sub> (mg/kg)</u>
Mouse*	8	P.O.	1	1,700 (1,546-1,870)
	8	i.p.	1	1,060 (982-1,145)
	10	i.p.	-	832
	10	S.C.	-	860
	5	i.v.	-	>400
Rat*	8	P.O.	1	1,530 (1,224-1,913)
	8	i.p.	1	790 (738-845)
Rabbit	4	i.p.	1	1,200 (952-1,612)

Footnote

- \* Death by respiratory failure followed by circulatory collapse.
- \*\* Apparently females only used.

Judged by LD50 values and doses producing ataxia, valproic acid is of intermediate toxicity compared with phenobarbitone, phenytoin, troxidone and phenacemide.

17. REPEATED DOSE TOXICITY STUDIES (Vol 1)

Only minimal data is presented.

i) Mouse (pp. 241-243)

Swiss; females only.

Groups of 30 given 0,50,400 or 800mg/kg/day i.g. 5 days/week.

Top Dose  
.....

23 deaths by day 4. After 10 days 2 surviving animals autopsied: no macroscopic or microscopic lesions.

Middle Dose  
.....

9 deaths by 23 weeks. Autopsy of remaining animals: no macroscopic

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or microscopic abnormalities.

Bottom Dose  
.....

For 46 weeks. No difference from controls in mortality, weight gain,  
macroscopic or microscopic findings.

ii) Rabbit (pp. 246-247)  
4 males, 4 females dosed orally with 200mg/kg/day for 21 weeks. No

control group. No abnormalities

Mortality: 2. Three females littered in 4th month. No abnormalities  
macroscopically or microscopically.

iii) Guinea Pig (pp. 243-246)

a) Oral Dosing  
Unbalanced groups of 5-10 animals given 0, 50, 200 or 500mg/kg/day 1-8.

for 17 weeks.

Half of 200mg/kg animals dosed b.d. 5/10 200mg/kg and 5/7

Mortality nil in control and low dose. end of study.

at autopsy. NO DEF-

b) Intraperitoneal Dosing  
2 groups of 10 animals dosed i.p. for 60 days with 0 or 100mg/kg.  
Mortality nil. No differences between groups in weight gain,  
haematology, microscopic or macroscopic findings.

18. TERATOLOGY (Vol 1)

i) Mouse (pp. 287-305)  
R.A.P. mice (n=31-36) given 0, 30 or 90mg/kg of drug in diet for  
8 days before mating and throughout gestation until littering.  
Maternal  
.....  
Pregnancy rate high in all groups. Foetuses/litter variable in all  
groups, lowest in controls (5-6/litter). Time to littering extremely  
variable (20-56 days in controls).

Foetal  
.....  
No differences between groups in mortality or body weight at birth  
and at 30 days.

No malformations but "morphological aspect" only examined.

OTHER NAMES

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ii) Rat (pp. 306-347)

Wistar rats (n=31-35) given 0, 30 or 30mg/kg 1.6 from 8 days before mating up to caesarean section (10 rats/group, day 21) or littering.

Maternal  
.....

foetuses/litter, resorptions and average placental weights comparable between groups at caesarean section.

At birth, foetuses/litter lowest in controls. Time to littering extremely variable (controls 22-55 days).

Foetal  
.....

No malformations by gross morphological examination at caesarean.

No drug-related differences in foetal mortality or body weight up to 30 days after birth. No malformations by gross morphology; no differences in weights of major organs at autopsy.

iii) Rabbit (pp. 348-367)

15 NZW given 45mg/kg orally from 3 days before mating and throughout gestation to caesarean section (day 29). 10 control animals.

No differences between groups in pregnancy rate, foetal weights or

whereas resorptions higher in control.  
Fetuses adequately examined by dissection and alizarin; two major malformations in treated group (cleft palate; coxo-femoral luxation), one in control (coelosomia, aberrant tail. and hind limbs) considered spontaneous.

CLINICAL STUDIES

19.

A. Volunteers (Vol, 1)

Caille (pp. 369-407)

Double-blind, cross-over study of 225-1000mg/day of valproic acid in 3 normal and 3 psychiatric "volunteers".

2/6 had diarrhoea; further 2/6 had tachycardia of 20 beats/min.

No significant change in EEG, wakefulness or urinary steroid excretion.

Poor study; poor translation.

B. Patients (Vol 2)

i) Mises (pp. 19-182)

Open study in 28 male and 45 female patients (38 children aged 9-15; 35 adults aged 16-80). All except two were confirmed epileptics, regularly receiving a variety of standard therapy.

400mg-1,400mg valproic acid for an average duration of 8 months (2-12 months) claimed to be effectively anti-epileptic; substituted completely for other anti-epileptic drugs in 21 patients and allowed dose reduction of standard drugs in most of remainder.

Other names

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Claim that overall results with valproic acid indicate improvement, 57.5% no change, 32.8% deterioration, 9.7%. Drug well-tolerated but "tendency to neutropenia".

This catalogue of case histories was apparently the "official clinical trial" for marketing clearance in France although providing no objective proof of either efficacy or side-effects.

~~ii)~~ Huertas (pp. 184-279)

Open study of valproic acid on aggressive behavioural disturbances in 27 epileptic and 8 non-epileptic mental patients. Initial daily dose 200mg, increased to 1200-1400mg (maximum 1800mg) for 2-13 months. Most patients concurrently treated with other anti-convulsant and psychoactive drugs.

Concluded valproic acid alone is insufficient to control epilepsy but is beneficial with barbiturates. On behavioural symptoms, reduction in dosage of neuroleptic drugs was possible. Tolerance good.

Another catalogue of case histories: objective assessment impossible.

iii) Various Authors (pp. 281-294)

Abstracts or brief assertions from 21 studies claiming effective anti-epileptic action, good tolerance and emphasising associated improvement of behavioural syndromes.

No objective data reported for assessment.

iv) Tchicaloff (pp. 296-307)

Open study in 104 in-patients with clinical and EEG evidence of epilepsy given 400-1,200mg/day of valproic acid for up to 14 months.

All patients were under treatment with other drugs: valproic acid in most cases enabled doses of standard drugs to be reduced or replaced.

Results were 53 "very satisfactory"; 37 "satisfactory"; 8 "failures" and 6 "discontinued treatment" (g.i., 3; exacerbation of petit mal, 2; somnolence, 1).

Tolerance described as excellent; blood counts, liver enzymes and serum electrophoresis unaffected (no data given).

A less anecdotal but still subjective paper.

v) Matthes and Schmutterer (pp. 309-319)

Open study during 2½ years of up to 3g/day valproic acid (mean 800-1,200mg) in 40 patients with various types of epilepsy (in 36 additional to existing treatment, in 4 as the only drug).

Best results (8/11) obtained in petit mal (3 c.p.s.) with absences. Benefit in other epilepsies less certain. No psychotropic effect.

Apart from some gastric effects and somnolence, good tolerance claimed; no allergic, haematological or renal toxicity, but no data given.



In animals, its anti-convulsant potency is generally less than phenobarbitone, phenacemide or phenytoin and greater than troxidone. It seems to act by raising brain GABA levels consequent upon inhibition of GABA-T.

Only minimal data is provided of repeated dose toxicity studies in mouse, rabbit and guinea-pig. No further information has been requested from the manufacturer because the design and scope of the experiments are inadequate to provide evidence on the potential hazard of the drug in man.

Teratology studies were made in three species at one or two dose levels, the highest of which was only three times the recommended maximal human therapeutic dose of 30mg/kg. The timing of drug administration seems to have aimed at a combined fertility/teratogenic study but, in general, the data falls far short of the normal standards for either.

Apart from the trial by Zelvelder (19, B, vi) the clinical studies are largely anecdotal and fail to provide objective evidence of efficacy or safety.

--- Other names

- 12 -

RECOMMENDATION

21

The Committee may feel that a Product Licence should not be granted because of

- i) inadequate toxicological and teratological data in animals,
- ii) inadequate evidence of efficacy and safety in clinical studies.

ABW.

Document 3 – Labazene Product Licence 1972

<p>PL/0623/0001 PL/0623/0002</p> <p>Pharmacy Products UK Ltd</p> <p>Labazene Tablets " Solution (Anti-Convulsant)</p>	<p><u>Sub-Committee on Toxicity and Clinical Trials (January 1972)</u></p> <p>The Sub-Committee recommends that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.</p> <p><u>Remarks</u></p> <p>Further toxicological and teratological data is also required.</p> <p><u>Main Committee (January 1972)</u></p> <p>The Committee agreed that a decision on these products should be deferred pending discussion with the applicants as to whether they would be prepared to conduct clinical trials comparing the product with phenytoin, since evidence of efficacy and safety in the clinical studies is inadequate.</p> <p>Subject to the applicant being willing to undertake a clinical trial on the lines indicated, then issue of a certificate could be recommended without further reference to the Committee.</p> <p><u>Sub-Committee on Toxicity and Clinical Trials (May 1972)</u></p> <p>On the evidence before them the Sub-Committee are unable to advise the grant of product licences for these preparations for the purposes indicated in the application since the animal toxicology, including teratology provided is inadequate, and the data which has been presented gives ground for concern in view of the expected long term administration of the drug.</p> <p><u>Sub-Committee on Toxicity and Clinical Trials (June 1972)</u></p> <p><u>Tablets - PL/0623/0001</u></p> <p>On the evidence before them the Sub-Committee recommend the grant of a product licence for one year for this preparation for the purposes indicated in the application provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy, and subject to all patients being monitored for therapeutic efficacy and safety.</p> <p><u>Solution - PL/0623/0002</u></p> <p>The Sub-Committee recommend that a decision on this product should be deferred pending the outcome of discussions between the Sub-Committee on Chemistry and Pharmacy and the applicant on the question of the "dropper" for use with this preparation.</p> <p>21</p>
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PL/0623/0001  
PL/0623/0002

Pharmacy Products UK Ltd

Labazene Tablets  
" Solution  
(Anti-Convulsant)

Sub-Committee on Toxicity and Clinical Trials

(January 1972)

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Remarks

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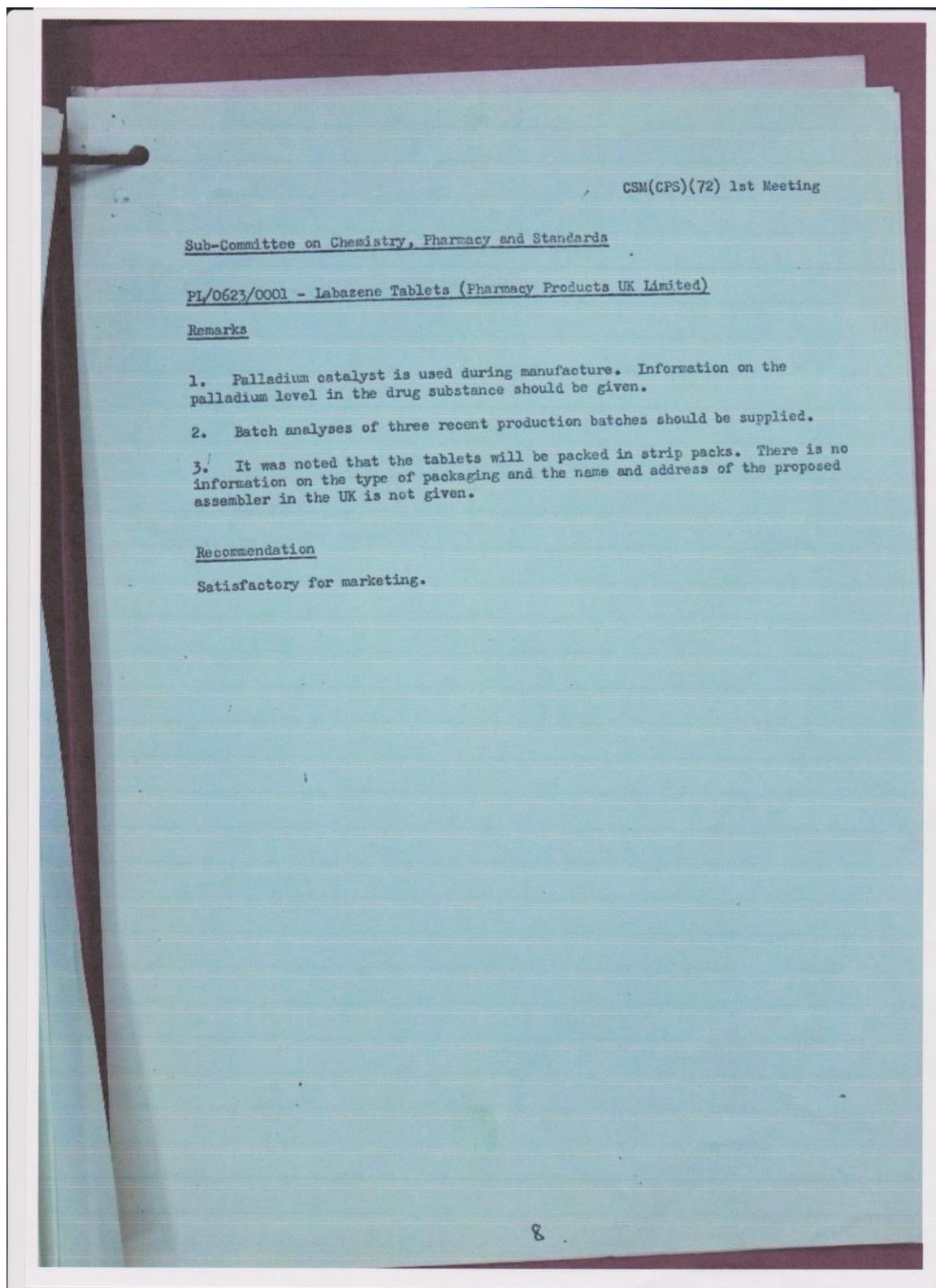
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Sub-Committee on Toxicity and Clinical Trials

(May 1972)

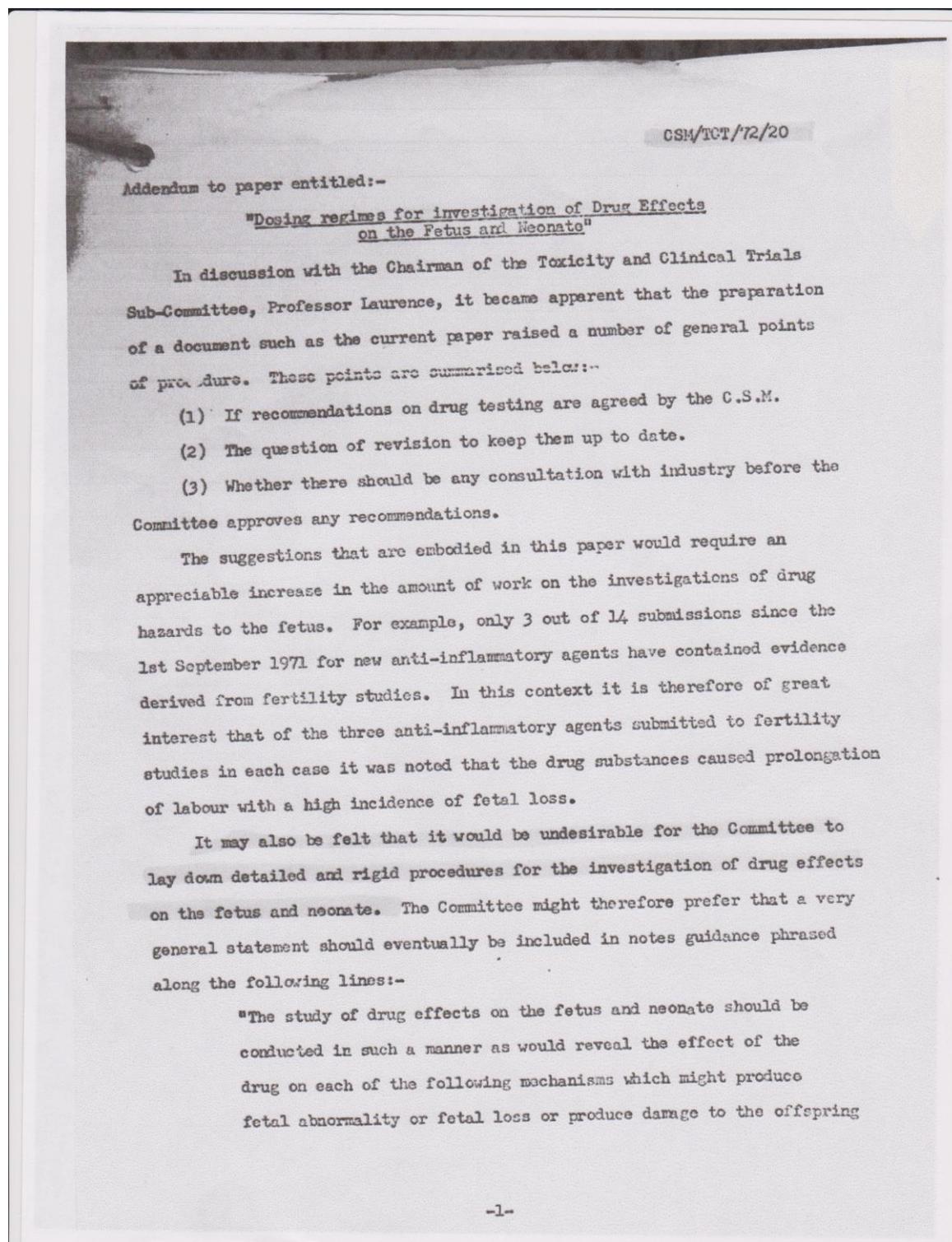
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Document 4 – Labazene Licence Granted 1972



## Document 5

### "Dosing Regimes for Investigation of Drug Effects on the Fetus & Neonate"



## Document 6 – CSM Minutes of Meeting 18<sup>th</sup> July 1973

NOT FOR PUBLICATION

CSM/AR/73/4th Meeting

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON ADVERSE REACTIONS

Minutes of the Meeting held on 18 July 1973

Present:

Sir Richard Doll (Chairman)  
Professor W I Cranston  
Dr D M Davies  
Professor D J Finney  
Professor R H Girdwood  
Dr M J Linnett  
Professor W W Mushin  
Professor D A Price Evans  
Professor D W Vere  
Mr F A S Middleton (Secretary)

Also Present:

Mr R E Tringham  
Dr A T B Moir  
Dr E L Harris )  
Dr A J Taylor )  
Miss M Edington )

DHSS  
SHHD  
Committee  
Secretariat

Dr W H W Inman )  
Dr M F Cuthbert ) Professional  
Dr G Greenberg ) Secretariat  
Dr A B Wilson )  
Mr A T Gray )

Contents

1. Apologies for absence
2. Minutes of the Meeting held on 16 May 1973
3. Matters arising from the minutes
4. Professional Secretariat's Report
5. Sudden Deaths and Phenothiazines
6. MAOI's and Tricyclic Antidepressants
7. Interactions between MAOI's and L-Tryptophen
8. Visual Disturbances with Ospolot
9. Dangers of Corn Starch in Aural Insufflation
10. Tetracyclines and Tooth Discolouration
11. Review of Recommendations
12. Adverse Drug Interactions booklet
13. Drug Dictionaries
14. Maxolon - dosage recommendations
15. Reports of Ocular Adverse Reactions
16. Advice from outside experts
17. Breast Atrophy and Oestrogen Therapy
18. Items for information
19. Date and time of next meeting

3.9 Drug Formulations (Minute 7 of 73/3)

The Chairman reported that the Main Committee had considered Mr Barrett's paper and had also commented on the difficulties associated with the problems to which Mr Barrett has drawn attention. They had decided to refer the paper to the Sub-Committee on Chemistry and Pharmacy for their consideration also, with a view to consultation with the ABPI on what might be done; one possibility being a communication to the BMJ on the matter.

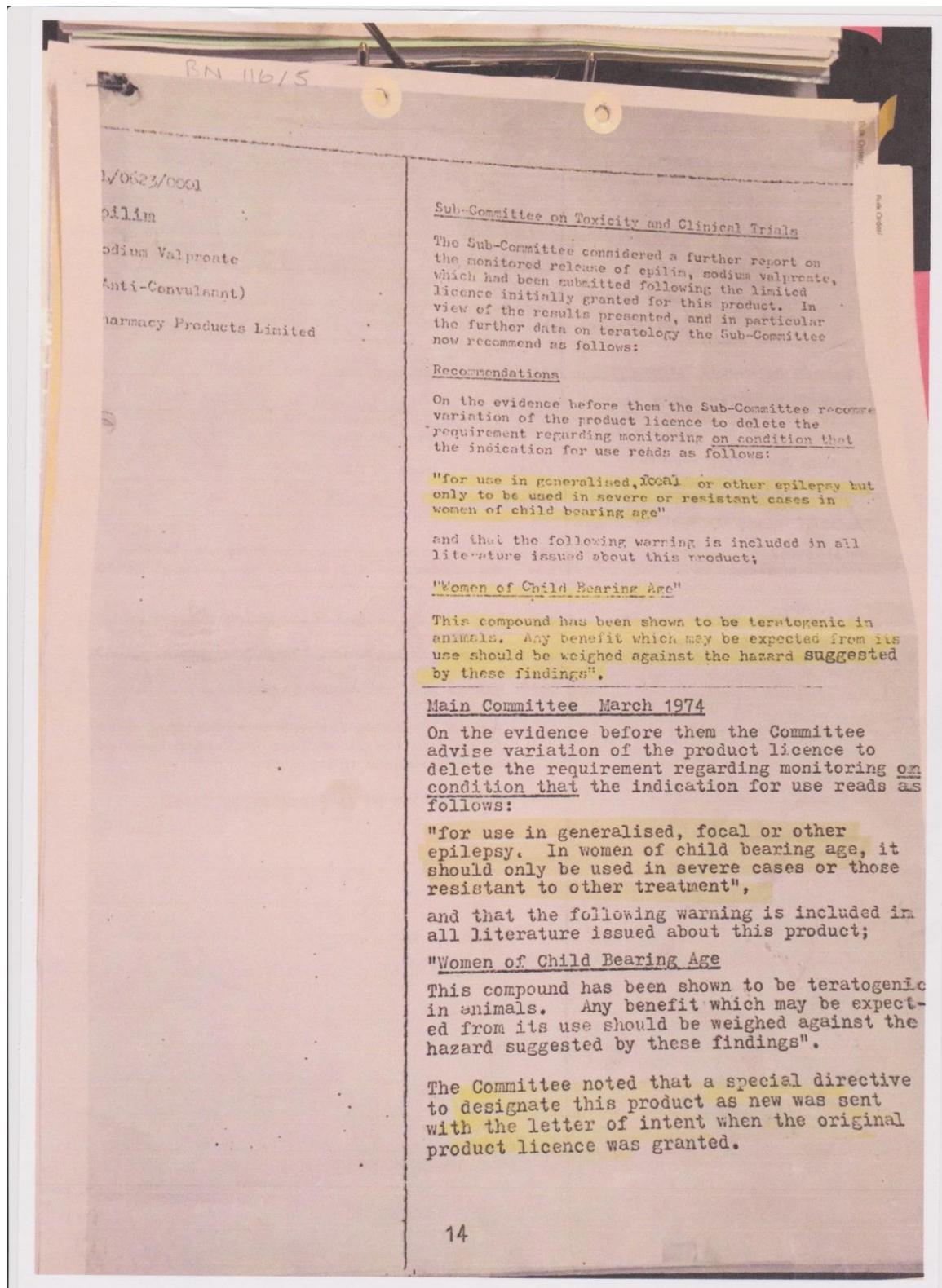
3.10 Anticonvulsant Teratogenicity (Minute 8 of 73/3)

The Committee was informed that the Main Committee had also welcomed the action by ICI Ltd but had thought the evidence not sufficiently conclusive to require all other manufacturers of anticonvulsant products to use a similar statement, especially as it could give rise to fruitless anxiety. The Sub-Committee believed, however, that the character of the evidence was strong enough for an assurance to be given to the Main Committee on that account, but accepted the point regarding anxiety. Nevertheless, they thought it would be best if prescribers were all made aware of the nature of the evidence and recommended that a statement similar to that proposed by ICI could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients themselves seeing it.

It was also agreed that a mention could be included in the next letter from Chairmen to all doctors.

## Document 7 – Product Licence Epilim 1974

### Changes to Recommendations.



## Document 8 – Data Sheet Epilim 1974

### DATA SHEET

#### NAME OF PRODUCT

Epilim

#### PRESENTATION

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

#### USES

For use in generalised, focal or other epilepsy (e.g. Petit Mal, Grand Mal, Mixed and other Psychomotor epilepsy).

In fertile women inadequately controlled by other therapies, the probable benefits of Epilim should be weighed against the possible hazard during early pregnancy suggested by laboratory experiments in animals (see Precaution - Women of Childbearing Age).

#### DOSAGE AND ADMINISTRATION

Adults and Children over 15 yrs.

Epilim can be introduced alone or added to existing treatment.

##### New Patients:

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

##### Patients receiving other Therapy:

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

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

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

##### Children under 15 years and Infants.

Dosage should be related to age within the range as follows:

0-3 years: Usually 20-30 mg/kg/day.

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

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

## CONTRA-INDICATIONS AND PRECAUTIONS

### CONTRA-INDICATIONS

There are no specific contra-indications for Epilim but note should be taken of the following precautions.

### PRECAUTIONS - GENERAL

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

#### Combined Medication:

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

#### Diabetic Patients:

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

#### Overdosage:

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

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

### PRECAUTIONS - WOMEN OF CHILDBEARING AGE

In animals, this compound has demonstrated teratogenic properties in laboratory experiments. Any benefit from its use should be weighed against the possible hazard suggested by this finding.

Standard teratological studies suggest that other anticonvulsants such as phenytoin may have some adverse effect on foetal development. In view of this, care should be taken in prescribing all anticonvulsant compounds including Epilim to epileptic women who may become pregnant.

### PRECAUTIONS - PHARMACEUTICAL

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

### LEGAL CATEGORY

Prescription only medicine.

### PACKAGE QUANTITIES

Carton containing 100 tablets in foil.

#### FURTHER INFORMATION

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

Clinically Epilim is effective in treatment of Petit Mal, Grand Mal, Mixed Epilepsies, and those with Temporal Lobe (or Psychomotor) components.

#### PRODUCT LICENCE HOLDER

Reckitt-Labaz

#### MANUFACTURERS

Reckitt & Colman Pharmaceutical Division,  
Hull HU8 7DS

#### PRODUCT LICENCE NUMBER

0623/0001

#### DATA SHEET REFERENCE

This Data Sheet was printed in June 1974.

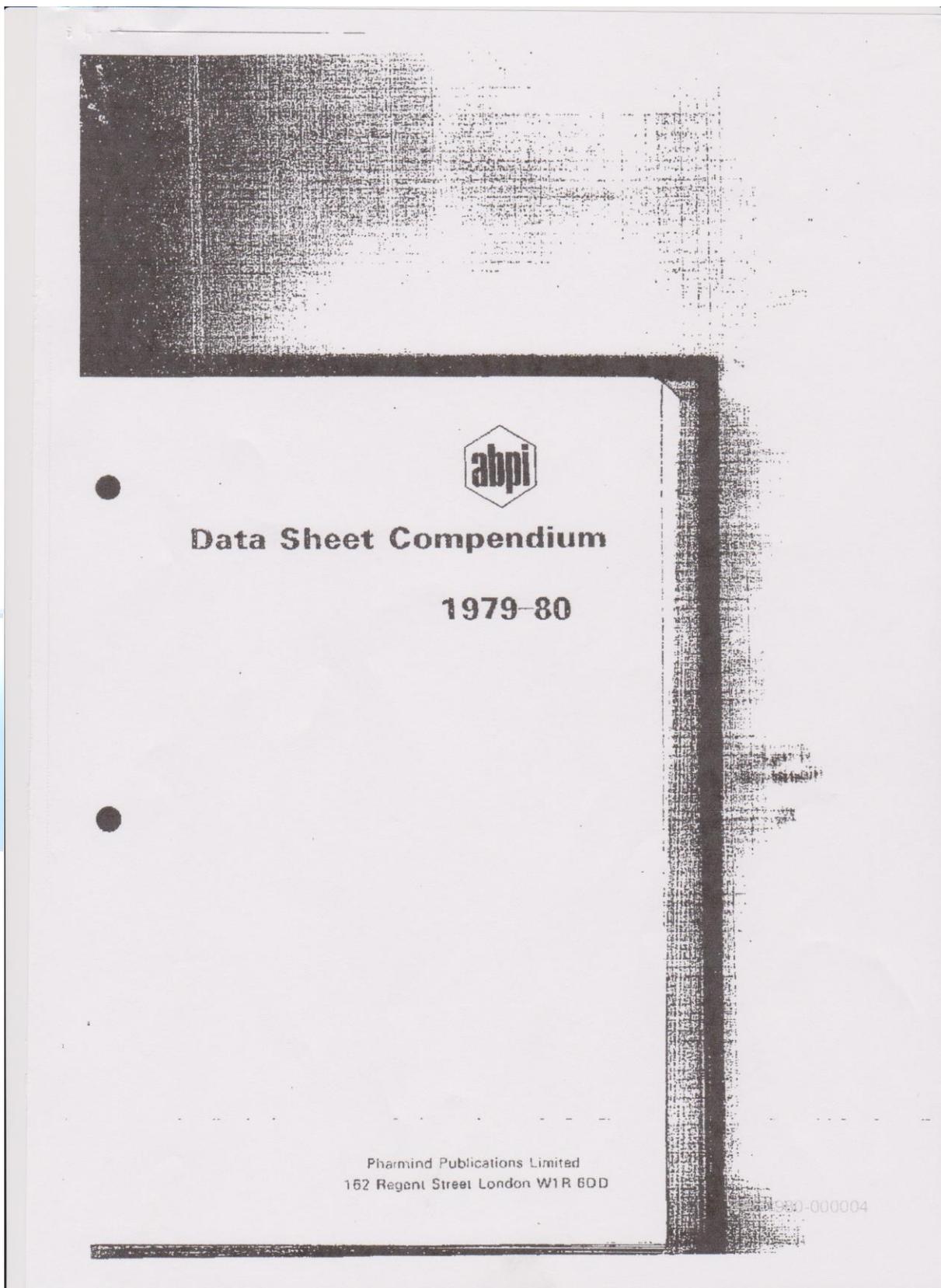
Further information is available on request from:  
Reckitt & Colman Pharmaceutical Division  
Hull HU8 7DS Tel: 0482 26151

Printed in Britain

'Epilim' is a registered trade mark

EP/1/74J

Document 9 – ABPI Data Sheet Compendium 1979 (Epilim)



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



**EPI-LIM**

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

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

**Dosage and administration** Epilim should preferably be taken with or after food. Both presentations of tablet should be swallowed whole. It is recommended that the 200mg tablet be used until the patient is stabilized. Epilim 500 enteric-coated is recommended for long-term treatment. Once the optimum dosage has been established.

**Adults** Dosage should start at 600 mg/day, in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range 1,000-1,800 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2,800 mg/day, or one other antiepileptic agent may be added, at a low dose, if patients already receiving other therapy. The same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined level. Sedation may be found possible to maintain control with Epilim alone.

**Children over 20 kg:** Initial dosage should be 400 mg/day (respective of weight) in divided doses, with spaced increases until optimum control is achieved; this is usually within the range 20-30 mg/kg of body weight per day.  
**Children under 20 kg:** 20 mg/kg of body weight, or 50 mg/kg/day.

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

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

**Contra-indications, warnings, etc.** There are no absolute contra-indications, but the following pre-

**Adverse reactions:** No renal or cardiac effects attributable to Epilim have been reported. Minor, gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by adding Epilim tablets to syrup with or after food, or by transferring tablets to syrup, which can be relieved by standard medication.

Transient hair loss has been noted in some patients. Tremor has occasionally been observed at dosage levels which may be controlled by reduction of dosage. Rarely, but usually, thrombocytopenia and thrombocytopenia have been reported, but have usually been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigation. It is recommended that patients receiving Epilim should be monitored for major and minor bleeding.

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

**Combined medication:** Epilim is generally well tolerated in combination with other antiepileptic agents. However, the following compounds should be avoided between these compounds: (1) Phenytoin, because necessary to reduce the dosage of other drugs when adding Epilim to existing anti-convulsant therapy; (2) the sedative effects of barbiturates are found to be enhanced, dosage of these compounds should be reduced; (3) the effects of many other drugs. Epilim may reduce the effect of oral contraceptives containing (MAOI) and other antidepressants, and dosage of such compounds should therefore also be reduced.

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

**Overdosage:** Few cases of accidental overdosage have been reported. Symptoms of ingestion of more than 30 g has been unremarkable with good management. Epilim is absorbed very rapidly, so gastric lavage may be of limited value. However, as it is excreted almost entirely within 24 hours (70% in the urine), general supportive measures are recommended, with special attention to maintaining an adequate urinary output.

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

**Pharmaceutical precautions** Epilim tablets are

until taken, they should be stored in a cool, dry place. Syrup should be kept cool and away from direct sunlight.  
 Caution: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrups containing SO<sub>2</sub> as a preservative should be avoided. The diluted product will have a 14-day shelf-life.

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

**Further information** Epilim represents a new approach in the therapy of epilepsy. Its simple chemical structure, free from nitrogen, differs widely from that of other currently available anticonvulsant drugs, and biological studies suggest that it may have a different mode of action, producing a rise in the level of GABA, the major inhibitory transmitter in the brain. There is no simple correlation between GABA and convulsive activity, evidence linking them is growing. Epilim is clinically effective in the treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe, or psychomotor, component.  
**References:** *Annals*, P. M. & Clark, J. E. (1974). *Brit. J. Clin. Pharmacol.* 5, 584-6.  
 Barnes, S. E. & Bower, B. D. (1975). *Develop. Med. Child Neurol.* 17, 175-81.

**Richens, A. & Ahmad, S. (1975).** *Brit. med. J.* 4, 255-6.  
 Haigh, D. B. & Fawcitt, W. I. (1975). *Develop. Med. Child Neurol.* 17, 743-8.  
 Clark, J. E., Clark, P. M., Clark, J. E. & Maheshwari, M. C. (1977). *Develop. Med. Child Neurol.* 19, 9-25.  
**Clinical & Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy** (Proceedings of a symposium held at Nottingham University Sept. 1975), MCS Consultant, England, 1976.

**Product licence numbers**  
 Epilim Tablets 0623/0001  
 Epilim 500 Enteric-coated Tablets 0623/0005  
 Epilim Syrup 0623/0004

Document 10 – Patient Information Leaflets Epilim (Sanofi)

1995 – 2001

305/028



## What you should know about **Epilim® Enteric Coated**

**Sodium Valproate BP**

**Please read this carefully before you start to take your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.**

The name of your medicine is Epilim. It contains Sodium Valproate. This is one of a group of medicines called "anticonvulsant or anti-epileptic agents" which are used to treat epilepsy.

**Things to remember about Epilim**

- 1. Before taking your medicine read the back of this leaflet.**
- 2. Take your medicine as directed by your doctor. Read the instructions on the label carefully.**
- 3. Epilim can sometimes cause side effects. See "After taking your medicine" on the back of this leaflet.**
- 4. Do not stop taking your medicine suddenly. Ask your doctor first.**
- 5. Tell medical staff you are taking this medicine, for example, if you go into hospital or see a dentist or another doctor.**
- 6. If you are likely to become pregnant, tell your doctor.**

You will find more about Epilim on the back of this leaflet.

Continued from overleaf

#### BEFORE TAKING YOUR MEDICINE

If you have liver disease DO NOT take Epilim without first talking to your doctor again.

If you can answer YES to any of the following questions tell your doctor. He may need to give you special instructions.

Are you pregnant or likely to become pregnant?

Are you diabetic?

Are you taking any other medicines to control your epilepsy?

Are you taking any medicine to reduce blood clotting (eg anticoagulant, aspirin)?

Are you taking antidepressants?

#### TAKING YOUR MEDICINE

Take your medicine regularly, as directed by your doctor. This is particularly important with anticonvulsants to make sure that you are getting the best control from your medication.

Look at the label on your medicine, it will tell you when to take it. If it does not, or you are not sure, ask your doctor or pharmacist for advice.

Swallow the tablets whole with a drink of water, usually after meals.

If you forget to take a dose at the correct time take it as soon as you remember then go on as before.

If you accidentally take an overdose contact your nearest hospital casualty department or tell your doctor immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

#### AFTER TAKING YOUR MEDICINE

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver in a very small number of patients. You should tell your doctor

IMMEDIATELY if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, loss of appetite, jaundice or worsening of your epilepsy.

Epilim may sometimes cause minor stomach upsets, increased appetite or weight gain. You need only consult your doctor about these if symptoms become troublesome.

Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before.

Epilim can also have other effects. You should report any of the following symptoms to your doctor.

Severe stomach pains

Abnormal bleeding or a tendency to bruise more easily

Shakiness or problems with balance

A rash or anything else which is unusual or unexpected

Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

#### STORING YOUR MEDICINE

Keep your tablets in a safe place where children cannot reach them; your tablets could harm them. Keep your tablets in the protective foil until you are ready to take them. If you remove them from the foil too soon they will spoil!

If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist. Only keep them if your doctor tells you to.

#### WHAT'S IN YOUR MEDICINE

Epilim Enteric-Coated tablets are lilac and come in two sizes containing 200mg or 500mg Sodium Valproate. They contain colour and other inactive ingredients including E123 (Amaranth).

This leaflet provides a summary of the information available on your medicine. For further information, consult your doctor or pharmacist.

#### THIS LEAFLET APPLIES TO EPILIM ENTERIC COATED TABLETS ONLY

**REMEMBER: This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.**

This leaflet has been produced in accordance with guidelines issued by the Association of the British Pharmaceutical Industry.

Made in England by:  
Sanofi Winthrop Ltd  
One Onslow Street  
Guildford, Surrey  
GU1 4YS

Sanofi Winthrop Ireland Ltd  
Ponsonby Road  
Dun Laoghaire  
Ireland



1995

1996



# What you should know about Epilim® Enteric Coated

Sodium Valproate BP



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4. Do not stop taking your medicine suddenly. Ask your doctor first.
5. Tell medical staff you are taking this medicine, for example, if you go into hospital or see a dentist or another doctor.
6. If you are likely to become pregnant, tell your doctor.

You will find more about Epilim on the back of this leaflet.

Continued from overleaf

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Are you taking antidepressants?

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Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim.

Epilim can affect the liver in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, loss of appetite, jaundice or worsening of your epilepsy.

Epilim may sometimes cause minor stomach upsets, increased appetite or weight gain. You need only consult your doctor about these if symptoms become troublesome.

Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before.

Epilim can also have other effects. You should report any of the following symptoms to your doctor.

Severe stomach pains

Abnormal bleeding or a tendency to bruise more easily

Shakiness or problems with balance

A rash or anything else which is unusual or unexpected

Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

#### STORING YOUR MEDICINE

Keep your tablets in a safe place where children cannot reach them; your tablets could harm them.

If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist. Only keep them if your doctor tells you to.

#### WHAT'S IN YOUR MEDICINE

Epilim Enteric-Coated tablets are lilac and come in two sizes containing 200mg or 500mg Sodium Valproate. They contain colour and other inactive ingredients including E123.

This leaflet provides a summary of the information available on your medicine. For further information, consult your doctor or pharmacist.

#### THIS LEAFLET APPLIES TO EPIILIM ENTERIC COATED TABLETS ONLY

**REMEMBER: This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.**

This leaflet has been produced in accordance with guidelines issued by the Association of the British Pharmaceutical Industry.

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Manchester, M23 9NF  
England



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## EPILIM® CHRONO CONTROLLED RELEASE

(Sodium valproate/valproic acid)  
PATIENT INFORMATION LEAFLET

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist. The name of this medicine is Epilim Chrono Controlled Release tablets.

### WHAT IS THIS MEDICINE?

Each Epilim Chrono 200 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 200mg sodium valproate.  
Each Epilim Chrono 300 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 300mg sodium valproate.  
Each Epilim Chrono 500 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 500mg sodium valproate.  
Each tablet contains Hypromellose, hydrated silicon, ethylcellulose, titanium dioxide (E171), erythrosine (E127), indigo carmine (E132), Black iron oxide (E172) and Macrogel 400.  
Epilim Chrono tablets are supplied in clear, white, round tablets and are supplied in cartons of 100.  
Epilim Chrono is an antiepileptic.

Product Licence holder:  
Sanofi-Synthelabo  
PO Box 597  
Guildford  
Surrey

Manufactured by:  
Fawcett Manufacturing Centre  
Edgelyde Avenue  
Farnham, Newcastles-upon-Tyne  
Tyne and Wear  
NE3 3TT

### WHAT IS THIS MEDICINE FOR?

Epilim Chrono is used to treat epilepsy (fits). Epilim Chrono is made so that the medicine in the tablet is released slowly over a long period of time.

### BEFORE TAKING THIS MEDICINE

Epilim should not be taken by patients with:

- a fit history
- a fit history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria (a rare metabolic condition)

If you have lupus (an inflammatory skin disease), please tell your doctor before taking Epilim. Your doctor may wish to do tests before you start your treatment and for the first six months of treatment.

If you are diabetic Epilim Chrono may make urine tests give false results.

### Epilim Chrono and Pregnancy

It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormally than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folic acid may lower the risk of having a baby with spina bifida. There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.

**Breast feeding:** - very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

If taken with some other medicines the effects of Epilim Chrono or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, trimoprim and meprobamate - antibiotics
- mifepristone - used to prevent malaria
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- iron/zinc/magnesium supplements - used to treat iron deficiency

Taking Epilim with chloroquine, which is used to prevent or treat malaria, may make it more likely that you may have seizures. Before travelling you should discuss taking malaria tablets with your doctor or pharmacist.

When you first start taking Epilim or if you are taking it with other medicines you may notice some drowsiness, if affected you should not drive or operate machinery.

### TAKING THIS MEDICINE

The usual dose of Epilim Chrono is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

The usual dose will be determined by the doctor.

The usual dose of Epilim Chrono is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Epilim Chrono is not suitable for use in children under 20kg.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim Chrono than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim Chrono your doctor may increase the dose of Epilim Chrono by 5 to 10mg for each kg of body weight per day.

If you have kidney disease your doctor may prescribe a lower dose.

Swallow the tablets whole, (do not crush or chew them), with a drink of water, usually after meals.

If you forget to take a dose at the right time take it as soon as you remember then go on as before.

An overdose of this medicine may be dangerous. If you have taken an overdose tell your doctor or go to the nearest hospital casualty department immediately.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

### WHILST TAKING THIS MEDICINE

Make sure you keep your regular check-up appointments. They are very important as your dosage may need to be changed.

If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim Chrono.

Epilim can affect the liver (and rarely the pancreas). In a very small number of patients, you should tell your doctor IMMEDIATELY if you develop a sudden illness especially in the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), sweating of the legs or worsening of your epilepsy or a general feeling of being unwell. Particular care is needed in the case of children under 3 or those with other nervous system disease.

Epilim sometimes causes the following: nausea (usually relieved by taking tablets with or after food); vomiting; changes in the amount of ammonia in the blood (which may cause vomiting, shaky movements and an unawareness of your surroundings); vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching; increased appetite or weight gain. Occasionally Epilim can affect the hair. Any loss of hair is usually temporary but when it goes back it may be more curly than before. Very rarely it may also cause a change in women's periods, hearing problems, kidney problems, acne, increased hair growth in women or increased breast growth in men. If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome.

Epilim sometimes causes changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or tremors with balance. Rarely it may cause liver disease, confusion; hallucinations; seizures; change in mood, jerky muscle movements and loss of consciousness. Fits, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk. If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping the Epilim.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also, immune disorders have occurred rarely.

Do not take this medicine after the month shown on the pack.

Epilim Chrono tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Date of revision of leaflet: February 2001.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The British Epilepsy Association (telephone: 0800 800 5050) will also be happy to try and answer any general questions on epilepsy.

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# EPILIM® CHRONO CONTROLLED RELEASE TABLETS (Sodium Valproate/valproic acid) PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- It is essential that you follow your doctor's advice.
- If you are helping someone else to take Epilim Chrono Controlled Release Tablets, read this leaflet carefully before you give them the first dose.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

**In this leaflet:**

1. What are Epilim Chrono Controlled Release Tablets and what are they used for?
2. Before you take Epilim Chrono Controlled Release Tablets
3. How to take Epilim Chrono Controlled Release Tablets
4. Possible side effects
5. Storing Epilim Chrono Controlled Release Tablets

Each Epilim Chrono 200 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 200mg Sodium Valproate.

Each Epilim Chrono 300 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 300mg Sodium Valproate.

Each Epilim Chrono 500 tablet contains a mixture of Sodium Valproate and Valproic Acid equivalent to 500mg Sodium Valproate.

You also contain hypromellose, hydrated silica, ethylcellulose, titanium dioxide (E171), erythrosine (E127), indigo carmine (E132), black iron oxide (E172) and Macrogol 400.

Product Licence Holder: Sanofi-Synthelabo, PO Box 597, Guildford, Surrey

Manufactured by: Fawdon Manufacturing Centre, Edgefield Avenue, Fawdon, Newcastle-upon-Tyne, Tyne & Wear, NE3 3TT.

**1. WHAT ARE EPILIM CHRONO CONTROLLED RELEASE TABLETS AND WHAT ARE THEY USED FOR?**

Epilim Chrono is an antiepileptic, which is used to treat epilepsy (fits).

Epilim Chrono tablets are oval shaped, lilac coloured tablets and are supplied in cartons of 100 tablets. Epilim Chrono is made so that the medicine in the tablets is released slowly over a long period of time.

**2. BEFORE YOU TAKE EPILIM CHRONO CONTROLLED RELEASE TABLETS**

**Do not take Epilim Chrono if you have:**

- liver problems
- a family history of liver problems
- a known allergy to Epilim/sodium valproate or any of the other ingredients
- porphyria (a rare metabolic condition)

**Tell your doctor before starting Epilim Chrono if you:**

- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose

You should talk to your doctor or pharmacist even if you no longer have these conditions, but have had them in the past.

Your doctor may wish to do blood tests before you start taking these tablets and during the first six months of treatment.

**Taking/using Epilim Chrono Controlled Release tablets with food and drink**

Swallow the tablets whole, with a drink of water, usually after meals. Do not crush, or chew them.

Do not stop taking Epilim or change the number of tablets you are taking without first discussing this with your doctor, as this may lead to a recurrence of your symptoms.

**When special care with Epilim Chrono Controlled Release Tablets is needed**

- If you develop a sudden illness especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe

upper stomach pains, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your condition or a general feeling of being unwell. YOU SHOULD TELL YOUR DOCTOR IMMEDIATELY. Epilim can affect the liver (and rarely the pancreas) in a very small number of patients.

**If you have any of the following speak to your doctor before starting your tablets:**

- systemic lupus erythematosus (a rare disease)
- from any metabolic disorders, particularly hereditary enzyme deficiency disorders such as a urea cycle disorder because of a risk of increased ammonia level in the blood,
- impaired kidney function. Your doctor may want to monitor your blood valproate level or adapt your dose,
- an increased appetite and are putting on weight.

**Pregnancy**

**Information for Women who could become Pregnant**

Before you start treatment, your doctor should discuss with you the problems that may arise if Epilim is used in pregnancy.

Unplanned pregnancy is not desirable in women receiving Epilim. You should use an effective method of contraception and consult your doctor before planning pregnancy. Epilim has no effect on how well your oral contraceptive pill works.

It is known that women receiving Epilim during pregnancy have a higher risk than other women of giving birth to a child with an abnormality. The likelihood of abnormalities is increased if you are also taking antiepileptic medicines at the same time. These effects include:

- head and facial deformities including cleft palate - a gap or depression in the lip
- deformities of the bones including hip dislocation
- malformation of the limbs
- deformities of the urogenital tract including defects in the wall of the male urethra or vagina leading to an additional opening
- cardiovascular malformations, including heart defects
- defects in the lining of nerve tubes, such as holes or protrusions
- spina bifida

Women who take Epilim during pregnancy may be more likely to have a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. These can usually be detected in the first 3 months of the pregnancy using routine antenatal screening blood tests and ultrasound scans.

Some babies born to mothers who took Epilim during pregnancy may develop less quickly than normal and may require additional educational support.

There may also be blood clotting problems (such as blood not clotting or not clotting very well) in the new born babies or mothers who have taken Epilim during pregnancy. This may appear as bruising or a delay in the stoppage of bleeds.

It is important not to stop your Epilim suddenly as this is likely to result in a relapse of your symptoms.

**Information for Women who are planning to get Pregnant**

If you become pregnant or think you may be pregnant whilst taking Epilim, you must tell your doctor immediately. Consult your doctor before planning pregnancy in order to receive appropriate counseling and to allow your doctor to adapt your treatment and/or dosage and to adequately monitor your pregnancy. It is essential that you discuss your treatment with your doctor well before you become pregnant.

**Breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine. Very little Epilim gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

**Driving and using machines**

When you first start taking Epilim, or if you are taking it with other medicines, such as other antiepileptic drugs or benzodiazepines, you may notice some drowsiness. If affected you should not drive or operate machinery.

**Taking/using other medicines**

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine - even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.

If taken with some other medicines the effects of Epilim Chrono or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:

- colestyramine - used to treat high blood lipid (fat) levels
- antipsychotic agents (used to treat psychological disorders) - Epilim may increase the effects of these drugs.
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbital, lamotrigine, primidone, felbamate
- cimetidine - used to treat stomach ulcers

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- salicylates e.g. aspirin
  - erythromycin, carbapenem such as imipenem, panipenem and meropenem antibiotics
  - mefloquine and chloroquine - use to prevent and treat malaria - may increase the likelihood of a fit.
- Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
  - zidovudine - used to treat HIV and AIDS
  - temozolomide - used to treat cancer
- When used in combination with olanzapine the following effects may occur;
- neutropenia – a blood disorder leading to a reduced chance of fighting infection, tremor, dry mouth, increased appetite and weight gain, problems with speech or slurriness or extreme tiredness

### 3. HOW TO TAKE EPIILIM CHRONO CONTROLLED RELEASE TABLETS

Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim Chrono Controlled Release Tablets.

Swallow the tablets whole, (do not crush or chew them), with a drink of water, usually after meals.

Adults: The usual dose of Epilim Chrono is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Elderly: The usual dose will be determined by the doctor.

Children over 20kg: The usual dose of Epilim Chrono is based on the child's weight as an amount of Epilim for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Epilim Chrono is not suitable for use in children under 20kg.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Epilim Chrono than others to control their fits.

Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Epilim Chrono your doctor may increase the dose of Epilim Chrono by 5 to 10mg for each kg of body weight per day.

If you have kidney disease your doctor may prescribe a lower dose.

**If you take more Epilim Chrono Controlled Release tablets than you should:**

An overdose of this medicine may be dangerous. If you think you may have taken more Epilim Chrono than you should or someone else has taken some, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

**If you forget to take Epilim Chrono Controlled Release tablets:**

If you forget to take a dose at the right time, take it as soon as you remember, then go on as before.

However, you must not take two doses at the same time.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better, as this may lead to an immediate relapse. If you stop them your condition may get worse.

Make sure you keep your regular check-up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim Chrono.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Epilim Chrono can have side-effects. Rarely they are serious, most of the time they are not. Usually they are reversible. You may need medical treatment if you get some of the side effects.

**Tell your doctor IMMEDIATELY if you notice any of the following serious side effects. You may need urgent medical attention.**

- repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, severe upper stomach pain, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs, worsening of your epilepsy or a general feeling of being unwell.

Epilim Chrono Controlled Release Tablets can affect the liver (and rarely the pancreas) in a very small number of patients.

You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment.

If you experience any of these effects c: if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets.

• bizarre behaviour, an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. This can be associated with more frequent or severe fits; loss of drive, particularly if phenobarbital is taken at the same time or if the Epilim dose has been suddenly increased.

- blood clotting problems
- spontaneous bruising or bleeding
- blisters with skin detachment.

If you experience any of the effects covered in this section, you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

- nausea or stomach ache, vomiting, diarrhoea, especially when starting the treatment
- shakiness (tremor), drowsiness, unsteadiness when walking
- tiredness, confusion, hallucinations, change in mood
- jerky muscle movements

• skin reactions such as rashes, occur rarely but patients who are also taking lamotrigine may be more at risk

• nausea (usually relieved by taking tablets with or after food)

• changes in the amount of ammonia in the blood; vasculitis - inflammation of the blood vessels, you may notice pain, redness or itching

- any loss of hair is usually temporary but when it grows back it may be more curly than before
- changes in women's periods
- hearing problems
- acne

- increased hair growth in women
- increased breast growth in men
- allergic reactions
- swelling of the feet and legs (oedema)
- weight gain as your appetite may be increased
- kidney problems, bedwetting or increased need to pass urine
- immune disorders.

These effects usually reverse on stopping the Epilim Chrono Controlled Release Tablets.

Epilim Chrono Controlled Release Tablets may cause a decrease in blood sodium which can result in tiredness, weakness, dizziness, feeling faint/fatigued, nausea, vomiting and muscle cramps. Less commonly there may be bloating, swelling, lightness of the hands and feet, confusion and seizures. Sometimes it can cause changes in the blood, you may notice abnormal bleeding or a tendency to bruise more easily, severe stomach pains, shakiness or problems with balance.

### 5. STORING EPIILIM CHRONO CONTROLLED RELEASE TABLETS

Keep your medicine in a safe place where children cannot see or reach it.

Epilim Chrono tablets may spoil if not stored properly. It is very important to keep them in the foil until just before you take them. Store them in a dry place at less than 30°C.

Do not take this medicine after the month shown on the pack.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date of revision of leaflet, June 2005.

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There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:

**Epilepsy Action**, New Anstey House, Gate Way Drive, Yeasdon, Leeds, LS19 7XJ

Telephone: 0808 800 5050. Website: [www.epilepsy.org.uk](http://www.epilepsy.org.uk)

**National Society for Epilepsy (NSE)**, Chesham Lane, Chalfont St Peter, Bucks. SL9 0FJ

Telephone: 01494 601400. Website: [www.epilepsynse.org.uk](http://www.epilepsynse.org.uk)

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Tell your doctor or pharmacist if any of the following side effects get severe or last longer than a few days, or if you notice any of the following in this leaflet, especially when starting treatment. This may be helped by taking the tablets with food or taking the Epilim EC tablets instead.

- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in some people
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, but only if you need to pass urine more often than usual

**Blood tests**  
Epilim Chrono can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.  
Talk to your doctor or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

**5. How to store Epilim Chrono**  
Keep out of the reach and sight of children.  
Do not take this medicine after the expiry date shown on the blister and carton after EXP.  
The expiry date refers to the last day of that month.  
Do not remove the tablets from the foil until just before you use them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

**6. Further information**  
What Epilim Chrono contains  
Each 200mg sodium valproate and 500mg valproic acid, equivalent to 200mg of the active substance sodium valproate  
Each 300mg controlled release tablet contains a mixture of 198.8mg sodium valproate and 87.2mg valproic acid, equivalent to 300mg of the active substance sodium valproate

- Each 500mg controlled release tablet contains a mixture of 333mg sodium valproate and 145mg valproic acid, equivalent to 500mg of the active substance, sodium valproate
- The other ingredients are: hypromellose (E649), ethylcellulose, hydrated silica, titanium dioxide (E171), erythrosine BS, aluminium lake (E127), indigo carmine aluminium lake FD and C Blue No 2 (E132), iron oxide black (E172), macrogol 400

**What Epilim Chrono looks like and contents of the pack**  
Epilim Chrono tablets are oval shaped and lilac coloured. The tablets are supplied in blister packs of 100

**Marketing Authorisation Holder and Manufacturer**  
Sanofi-Aventis  
One Osney Street  
Oxford  
OX2 0EL  
UK

**Manufacturer**  
Fawdon Manufacturing Centre,  
Edgefield Avenue  
Fawdon  
Newcastle-upon-Tyne  
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UK

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

**This leaflet was last revised in 09/2007.**  
There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be contacted at:  
**Epilepsy Action**, New Anley House, Gate Way Drive, Yeovil, Somerset, BA8 2RN. Telephone: 0800 800 5050. Website: [www.epilepsy.org.uk](http://www.epilepsy.org.uk)  
**National Society for Epilepsy (NSE)**, Chesham Lane, Chalfont St Peter, Bucks, SL9 0JQ. Telephone: 01494 601400. Website: [www.epilepsynsociety.org.uk](http://www.epilepsynsociety.org.uk)

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Epilim® Chrono 200mg, 300mg and 500mg Controlled Release Tablets**  
sodium valproate

**sanofi-aventis**

**Is this leaflet hard to see or read? Phone 01483 505515 for help**

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

- What Epilim Chrono is and what it is used for
- Before you take Epilim Chrono
- How to take Epilim Chrono
- How to store Epilim Chrono
- Further information

**1. What Epilim Chrono is and what it is used for**

**What Epilim Chrono is**  
Epilim Chrono is a medicine called an anti-epileptic agent. It works by helping to calm the brain down.

**What Epilim Chrono is used for**  
Epilim Chrono is used to treat epilepsy (fits) in adults and children.

**2. Before you take Epilim Chrono**

**Do not take Epilim Chrono and tell your doctor if:**

- You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim Chrono (see section 6).
- You have had an allergic reaction to a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.

- You have liver problems or you or your family have a history of liver problems
- You have a rare illness called porphyria

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim Chrono.

**Take special care with Epilim Chrono**

Check with your doctor or pharmacist before taking this medicine if:

- You have diabetes. This medicine may affect the results of urine tests
- You have kidney problems. Your doctor give you a lower dose
- You have fits (epilepsy), brain disease or a metabolic condition affecting your brain
- You have a urea cycle disorder where too much ammonia builds up in the blood
- You have a disease called "systemic lupus erythematosus (SLE)" - a disease of the immune system which affects skin, bones, joints and internal organs

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim Chrono

**Weight gain**

Taking Epilim Chrono may make you put on weight. Talk to your doctor about how this will affect you.

**Blood tests**

Your doctor may wish to do blood tests before you start taking Epilim Chrono and during your treatment.

**Taking Epilim Chrono with other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. Some medicines may affect the way Epilim Chrono works. Also some medicines can affect the way Epilim Chrono works.

**The following medicines can increase the chance of you getting a rash or other allergic reaction:**

- Some medicines used for pain and inflammation (salicylates) such as aspirin.
- Some other medicines used to treat fits (epilepsy) - see page 2, section 3. Patients taking other medicines for "fits". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, lamotrigine and felbamate

**Epilim Chrono may increase the effect of the following medicines:**

- Medicines used for thinning the blood (such as warfarin)
- Zidovudine used to treat HIV infection
- Medicines used for depression
- Medicines for asthma
- Monamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

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### Additional Resources

The Commission for the Control of Epilepsy and its Consequences (1977) Workshop on antiepileptic drug development, April 15. Edited transcript. Department of Health, Education and Welfare (USA)

The Commission for the Control of Epilepsy and its Consequences (1977) Plan for Nationwide Action on Epilepsy. Volume II Part 2. Department of Health, Education and Welfare (USA)

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## ***OACS Ireland Submission to the UK Independent Medicines and Medical Devices Safety Review***

### **1. Introduction**

Concerns relating to Anti Epilepsy Drugs (AED's) and Fetal Anti-Convulsant Syndrome (FACS) have been growing steadily in recent years in many countries including in the UK and in Ireland.

OACS Ireland (Organisation for Anticonvulsant Syndrome) and the FACS Forum Ireland, an umbrella group of organisations which includes Epilepsy Ireland have been working to highlight the use of sodium valproate in women since 2013.

Our work has been centered around three main themes:

1. Working with relevant authorities including the Health Service Executive, Department of Health, the Health Products Regulatory Authority and the Pharmaceutical Society of Ireland to reduce the risks for current and future generations of children being born with severe physical and developmental disabilities associated with FACS;
2. Seeking adequate support for those already affected by FACS
3. Campaigning for an independent investigation/ inquiry on the historical use of Valproate including issues of accountability and redress.

To date, while there has been significant progress on Point 1 above and limited progress on Point 2, there has unfortunately been little progress on Point 3.

OACS Ireland has close working ties with the UK OACS Charity and in our submission, we have chosen not to repeat many of the well-established facts and background relating to the issue. Instead we are focusing on the current and historical Irish position below to highlight that FACS is an international tragedy and not just limited to the UK. We understand that Ireland is outside the jurisdiction of the Independent Medicines and Medical Devices Safety Review, but we fully agree with the OACS UK submission to the Review and support the calls for action highlighted therein.

## **2. OACS Ireland**

Since 1999 OACS UK has supported UK families to provide support and raise awareness, for children affected by Fetal Anticonvulsant Syndromes (FACS) OACS Ireland is a branch of OACS UK; it has a similar remit and provides support and representation for families in the Republic of Ireland and Northern Ireland.

We want to ensure that people living with FACS along with their families will experience better recognition, improved public health services and support.

OACS Ireland is a voluntary group, predominantly made up of mothers and fathers of children who have been affected. We are currently in the processing of becoming a registered charity in Ireland with the Charities Regulatory Authority. Many families in our organisation have received invaluable support from OACS UK over the years and we are indebted to the volunteers for this, as well as their ongoing encouragement in developing OACS Ireland.

In addition to our work in Ireland, OACS Ireland is also a stakeholder in the MHRA Valproate Stakeholders' Network (VSN), a relationship which has helped inform progress and practice in Ireland in recent years.

## **3. The FACS Forum Ireland**

FACS Forum Ireland is an umbrella group of organisations that have come together to:

- Advocate for better services and supports for families & children affected by Foetal Anti-Convulsant Syndrome (FACS); and
- Raise awareness of FACS and ensure that appropriate risk reduction measures are implemented in Ireland.

Members of the Forum include the Disability Federation Ireland (DFI); Epilepsy Ireland (EI); Genetic and Rare Diseases Organisation (GRDO); Medical Research Charities Group (MRCG); Organisation for Anti-Convulsant Syndromes Ireland (OACS Ireland); Migraine Association of Ireland (MAI) and Shine.

## **4. Valproate in Ireland**

Sodium Valproate (Epilim) is a drug licenced in Ireland for the treatment of epilepsy and bi-polar disorder. Developed in the 1960s, it has been authorised in Ireland since 1975. For many people, Sodium Valproate can be a very effective drug, in many cases the only effective drug.

However, the teratogenic effects of Valproate have been accepted since the mid-1990s, while effects on development were highlighted for over a decade prior to the publication of the NEAD studies from 2008.

Despite these risks, many parents involved with the OACS Ireland organisation and many more over the past 40 years were not informed of the risks, risk-reduction measures were not put in place and Valproate treatment continued as normal during

pregnancy. In this regard, the Irish situation is very similar to the experience in the UK.

#### **4.1 Total Valproate Prescriptions**

A 2017 Health Service Executive (HSE) report on the use of sodium Valproate in women (16-44 years) found that between January 2014 and July 2016, there was a decline in the total number of reimbursements from c.2,000 to c. **1,700** per month. While rates of prescribing fell for epilepsy, there appeared to be a rise in prescriptions for other indications.

See: *Prescribing trends for sodium valproate in Ireland*: [https://www.seizure-journal.com/article/S1059-1311\(16\)00041-8/pdf](https://www.seizure-journal.com/article/S1059-1311(16)00041-8/pdf)

#### **4.2 Children Affected**

There is no Irish data on how many children may have been affected by exposure to Valproate. Based on UK and international data, OACS Ireland estimates that there have been c. 30 Valproate pregnancies per annum, or over **1,000 since 1983**. This equates to c. **400** children with developmental delay/ autism/ ADHD and over **100** born with physical malformations. The HSE is currently undertaking a Rapid Assessment Report to establish more reliable data for Ireland.

#### **4.3 Confirmed Diagnoses of FACS**

There is no official data available for Ireland. However, the Department of Clinical Genetics, Our Lady's Children's Hospital Crumlin have indicated that **43** children have received a diagnosis of FACS via their service. This is confirmed in a recent study, "Fetal valproate syndrome: the Irish experience" published in The Irish Journal of Medical Science in 2018.

Hamizah Mohd Yunus & Andrew Green from the Department of Clinical Genetics, Our Lady's Children's Hospital, Crumlin stated: *"Another interesting fact that arose from our record is that the majority of the women have been on VPA [valproate] since diagnosed with epilepsy (mostly since childhood). The medication was not changed due to the stability of their condition... There was a big possibility that the patients were not aware regarding the higher dose of folic acid supplementation, the teratogenicity effect of the VPA and the need of contraception"*.

See: *Fetal valproate syndrome: the Irish experience*:  
<https://www.ncbi.nlm.nih.gov/pubmed/29396778>

### **5. Licensing history of Valproate in Ireland**

Licensing of medicines in Ireland is the responsibility of the Health Products Regulatory Authority (HPRA). The HPRA (formerly the Irish Medicines Board) predecessor organisation, the National Drugs Advisory Board (NDAB) was first established in 1966. Its early role included advising the Minister for Health, who undertook the competent authority role at that time. The general legislative framework for mandatory product authorisation in Ireland, was first introduced in October 1974, when an initial scheme for product authorisation was implemented

through S.I. No. 187/1974, the European Communities (Proprietary Medicinal Products) Regulations, 1974).

The first licence for a sodium valproate containing medicine, which involved an assessment by NDAB, was granted by the Minister for Health in January 1975. The 1975 licence was granted through S.I. No. 187/1974.

While Valproate was used in Ireland prior to 1975, its use was subject to clinical practice.

## **6. Valproate Warnings**

Information provided to professionals and patients in Ireland through Data Sheets/SPCs and Patient Information (package) leaflets has followed a similar course to that of the UK.

### **6.1 Data Sheets/ SPCs**

Early Product Authorisation documentation included a sentence that “in view of its teratogenicity in animals, it should not be used in pregnancy unless the physician considers it necessary”. This was expanded in 1983 indicating that “there have been some reports of congenital abnormalities in offspring of a small number of epileptic patients who were being treated with valproate. There is no clear evidence of a significant association. However, the physician should bear this in mind while also taking into account the effect of seizures during early pregnancy on the mortality and morbidity of the mother and of the foetus”. Similar information was presented in Data Sheet Compendiums in the mid-1980s. By the late 1980s, the language used was revised to state that “Some studies have demonstrated an increase in the expected incidence of congenital abnormalities... the extent of the relationship is as yet uncertain”. By 1991, the Data Sheets highlighted neural tube defects for the first time, estimating incidence at 1% and recommending monotherapy in pregnancy. It also stated that “patients should be informed of these [risks] and the need for screening”.

By the mid-1990s, other abnormalities were highlighted and both folate supplementation and the ‘lowest effective dose’ were recommended in women of childbearing age. In 2003, a new section was introduced recommending that “Epilim be used in women of child bearing age only in severe cases or those resistant to other treatment”.

In 2005, it was advised that “women of childbearing potential should not be started on Epilim without specialist neurological advice” and “Adequate counselling should be made available to all women with epilepsy... regarding the risks...”. If pregnancy is planned, consideration should be given to cessation of Epilim. Developmental Delay is also mentioned for the first time.

In 2006, a “very careful evaluation” is called for although “in certain cases Epilim may be an appropriate choice for women of childbearing potential provided that an informed choice has been made”. Autism Spectrum Disorders were first mentioned in 2009. In 2012, it is stated that “women of child bearing potential must use effective

contraception...”. It also states that “this medicine must not be used in women of child bearing potential unless clearly necessary”. In 2014, data from meta-analyses is included specifying the incidence of congenital malformations at 10.73%. From 2015, the data sheets contain expanded information in line with the European Medicines Agency decision the previous year.

## **6.2 Patient Information Leaflets**

OACS Ireland understands that the first Patient Information Leaflets (PILs) on valproate were in 1995. The 1995 PIL states “It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women”. The risk of spina bifida is highlighted at 1-2% and women are encouraged to take folate and to discuss treatment with their doctor if considering pregnancy or if pregnant.

In 2004, the information is revised. Contraception is advised and “unplanned pregnancy is not desirable”. Malformations other than spina bifida are included and polytherapy risk is explained. In 2006, epilepsy specialists are mentioned and for the first time, the risk of developmental delay. In 2009, the information is revised and a greater focus is placed on communications with the patient’s doctor and more information on potential disabilities is provided including “autistic disorders”.

From 2012, women of childbearing potential are advised not to take Epilim unless explicitly advised so by their doctor. From 2015, a new boxed warning is introduced at the beginning of the leaflet for the first time and more detailed information as mandated by the EMA ruling of 2014 is included.

OACS Ireland contends that the information provided to professionals and patients has lagged behind accepted knowledge and published data in the literature. In a recent BMJ paper, Prof Carl Heneghan concludes that “The signal of congenital malformations provided by the cumulative evidence in 1990 showed that there were problems, and by 2005 there could be no doubts whatsoever about the association”. See: Heneghan C, Aronson JK; Sodium valproate: who knew what and when? Cumulative meta-analysis gives extra insights. *BMJ Evidence-Based Medicine* Published Online First: 22 October 2018. The steps that have been taken since 2014 and more particularly from 2018, could and should have been taken much earlier.

We also note that a comparison of Irish and UK SPCs and PILs highlights that there are often delays of one or more years between a UK update and a similar update being made in Ireland.

## **7. The FACS Forum Campaign – What needs to happen in Ireland**

The FACS Forum has led on a campaign calling for action on three fronts:

- Put in place measures to support those who have been affected in the PAST
- Put in place services for families affected in the PRESENT
- Reduce the risk of children being born FACS in the FUTURE.

## **7.1 Put in place measures to support those who have been affected in the PAST**

The Forum is concerned that in Ireland, few efforts have been made by the State to determine the scale of the problem, investigate the reasons behind it or deal with issues of accountability. This is in contrast with other jurisdictions including the UK and France.

The FACS Forum has called for the following to be addressed urgently:

- To undertake a national study/ audit to identify cases of diagnosed and suspected FACS.
- To establish an independent investigation or inquiry into the historical use of Valproate, addressing:
  - If and how existing cases of FACS could have been prevented.
  - Whether or not appropriate and timely information was provided to healthcare professionals and to patients in line with knowledge at the time.
  - Whether or not appropriate decision-making processes were in place concerning the treatment of women taking Valproate in line with knowledge at the time.
  - Whether or not appropriate regulatory steps have been taken over time to ensure patient safety.
  - How a system of redress should be established to meet the lifelong care needs of children and the impact of diagnosis on families (in order to avoid the need for legal solutions for already burdened families).

The above concerns were highlighted to Minister for Health Simon Harris when the Forum met with him in March 2018 and also highlighted to a session of the Joint Oireachtas (Parliamentary) Committee in Health in May.

- To hold an Oireachtas Health Committee examination of the issue to include written and oral submissions from relevant stakeholders and including a final report to the Oireachtas.

### **7.1.1 Progress to date**

The HSE has established a Valproate Response Project which oversees eight different workstreams relating to the issue of Valproate. Representatives from the FACS Forum including OACS Ireland sit on the Project's steering group, project group and a number of the working groups.

One workstream has been responsible for producing a Rapid Assessment Report to quantify the extent of the problem. This report has been completed but has not yet been made public. The data is based on a variety of national and international datasets and while it estimates prevalence, it acknowledges that "the true impact of valproate on women and children will only become apparent as data is collected prospectively".

Regarding an independent investigation, The FACS Forum has received communication from the Minister for Health that indicates that he does not believe that an investigation regarding state accountability is required at this time.

OACS Ireland is left confused and disappointed by the Minister's response. Families need to know how so many cases of FACS was allowed to happen. The Irish public deserve answers too, so that changes can be put in place to avoid similar occurrences in future. A full investigation needs to take place so that the families can move forward knowing the truth. Families also need a system of redress established so that they can ensure that their children have the best of care and when families are no longer around to see their loved ones. Some of the complexities that arise in relation to the issue of compensation would also be best addressed via an investigation.

The FACS Forum including OACS Ireland addressed the Joint Oireachtas Committee on Health on the subject in May, alongside representatives of the HPRA and HSE. In June, the Committee published a report (attached) with 12 recommendations including:

- "The Committee recommends the establishment of an independent investigation to examine the historical use of valproate medicines in Ireland and into the ongoing effects of valproate medicines"
- "The Committee recommends that further consideration and examination is undertaken with regard to compensating FACS patients".

There has been little progress on these matters since June.

## ***7.2 Put in place services for families affected in the PRESENT***

Valproate-related disabilities are complex, wide-ranging and individual. Obtaining a diagnosis in Ireland is difficult, and treatment often involves attending a multitude of unconnected and uncoordinated specialist services. Often, families have more than one child affected, and in many cases, full-time caring is required. It is critical that appropriate supports are put in place for the children and families already affected.

This involves:

- A streamlined diagnostic pathway for cases of suspected FACS via Clinical Genetics or other appropriate services.
- Better diagnostic tools need to be developed to identify suspected cases and diagnostic capacity needs to be widened (e.g. to include paediatrics / neuropsychology or access to international expertise)
- A national register of affected individuals to better assess individuals' often complex needs
- Evaluate treatments; assess long term implications; improve co-ordination in services and plan health services more efficiently.
- A full audit of the needs of individuals and families affected by FACS, the services/ supports provided to them and how services can be best co-ordinated and delivered to meet needs.

### ***7.2.1 Progress to date***

The HSE has established a Valproate Response Project which oversees a number of work streams including:

- Ensuring that people who may have been impacted by current or historic risks of Epilim exposure in the womb are provided with immediate information and support. Women on valproate who could be identified under certain reimbursement schemes have been contacted directly by letter as well as their GPs on a named-patient basis. The letters encourage people to get in touch if they have any concerns over a previous pregnancy. A HSE helpline has been established to respond to public and professional enquiries.
- Work is underway in developing a diagnostic pathway for FACS. Funding for an additional Consultant Geneticist (and supports) has been secured.
- Initial meetings with families have been held to begin the process of scoping out the wide range of services needed.
- A commitment has been made in improving IT infrastructure including the Irish Epilepsy & Pregnancy Register, which it is hoped will act as a register of women on valproate and of individuals affected. Much work still needs to be done in this area.

### ***7.3 Reduce the risk of children being born FACS in the FUTURE.***

The Forum welcomed the February 2018 recommendations made by the European Medicines Agency (EMA) strengthening the risk reduction measures introduced in 2014. Since February, there has been significant progress in implementing the new measures in Ireland alongside additional measures not mandated by the EMA, but which were called for by OACS Ireland and the FACS Forum.

- Changes to the PILs and SPCs to reflect these new EMA conditions.
- Visual warning symbols on boxes and on blister packs agreed
- New patient information resources by HPRA and HSE
- Brand name Epilim used on all patient materials
- Actions taken on ending broken bulk dispensing – smaller pack sizes to be introduced
- The mandatory use of package inserts and reminder cards by pharmacies if dispensing in broken bulk. Clear expectations set by Pharmacy Regulator and a number of ‘concerns’ have been investigated where instructions have not been followed.
- Direct communication from HSE to women being prescribed the drug as well as their GPs. GPs asked to arrange appointments and specialist referrals. However, there have been difficulties in contacting the full cohort of women taking valproate.
- Point of care alerts in primary practice and pharmacy dispensing software
- A programme to implement best practice for women with epilepsy including access to monitoring and annual specialist review.
- Implementation of the HPRA guidance on the pregnancy prevention programme
- Funding for a research project from the Health Research Board to measure the effectiveness of risk reduction measures

## 8. Quotes from families affected

### **Mother from Cork**

*"I took Epilim when I was pregnant. My 5-year-old son has a diagnosis of childhood Autism. My son was non-verbal and he needed speech therapy he also needed and an OT assessment for his sensory needs now my 2-year old child has been put on the Autism Spectrum. None of these services were available to my son and my husband and I had to pay privately. The devastating impact this has had on our family is unthinkable to bear at times."*

### **Mother from Mayo**

*"Since the birth of my two children, never a month goes by without hospital or specialist appointments for my two children, they are 14 and 9, their disabilities range from global development delay, scoliosis, speech and language, dyslexia and physical difficulties. I had to resign in 2016 from employment to become a carer. Last December, my daughter wanted to end her life, this is the effect of sodium valproate".*

### **Mother from Dublin**

*"The impact that the lack of correct information Sodium Valproate had on my life has been incredible. Personally, the everyday guilt can be all consuming, and has me stuck in a vicious cycle of guilt. Every day the same questions loom... if only I had known? What could I have done differently if anything? Can I fix my girls now? What will their future hold? It's infuriating, it makes me nauseas with a mixture of emotions".*

### **Mother from Meath**

*"Behind all statistics are real human stories and mine is that I am the mother of three adult children who have all been affected by exposure to Valproate. We are living evidence of the risks and the devastating impact of this drug. 2 of my 3 boys require lifelong care and will never be able to have a normal life. They will never be able to get married. Never be able to have children. They have been robbed of all the joys of life. The effects of sodium Valproate have been unbearable".*

## 9. Conclusions

We want to thank the Review for the opportunity to contribute with the Irish experience. We hope to have highlighted that valproate is an international tragedy, and one which needs a thorough response not just in the UK, but around Europe and the world. We hope that the UK review will provide much needed leadership on this issue and pave a path for other governments in Europe, including Ireland to follow.

While Ireland has responded very positively in 2018 to risk reduction measures, there has been little progress in obtaining justice for the families affected over the past 40+ years.

The voices of families must be heard. We hope that the steps currently being taken in the UK can ultimately lead to a similar process being undertaken in Ireland.

**Epilepsy Action has received funding from pharmaceutical companies in the past. These include manufacturers of sodium valproate as listed below. We can provide more detailed information if required.**

**Reckitt-Labaz (manufacturers of Epilim)**

1979, British Epilepsy Association and Reckitt-Labaz (manufacturers of Epilim) cooperated to produce a film “Epilepsy – a label for life”.

**Sanofi Aventis (manufacturer of Epilim, sodium valproate)**

2005, £50,000 support to fund the Development Officer for Women post (two years' costs).

2007, £20,000 support to fund the Development Officer for Women post.

2008, £20,000 support to fund the Development Officer for Women post.

2009, honorarium plus expenses for S Wigglesworth for participating in Epilepsy Guidelines development meeting.

2010, £3,500 support, joint funding with another pharmaceutical company of “Don't sub my drugs” material

2010, £8,000 support for “epilepsy in the elderly” publication

2011, payment for an advert in the Guardian featuring Epilepsy Action's “Don't sub my drugs” campaign

2012, honorarium plus expenses for S Wigglesworth for participating in epilepsy guidelines development meeting.

2012, honorarium plus expenses for S Wigglesworth for participating in epilepsy advisory board meeting.

2012, £27,000 support development of an app for people with epilepsy

2014, £11,500 support to develop e-learning for practice nurses

2015, honorarium, plus expenses, for Nicole Crosby-Mckenna for participating in advisory board meeting.

**Desitin Pharma Ltd (generic manufacturer of sodium valproate)**

2014, £8,000 support to develop e-learning for practice nurses

There may be additional support from earlier years but such records are not retained.

# **Epilepsy Action evidence in response to the Independent Medicines & Medical Devices Safety Review**

## **October 2018**

### **Summary**

Strong clinical evidence of the risks associated with pregnancy and sodium valproate exists. The risk is high when compared to other epilepsy medicines or to women not taking epilepsy medication. A link between sodium valproate and teratogenicity was indicated on patient information leaflets as early as 1974 and the body of evidence confirming this link has increased over time. But some women remain unaware.

Pre-conception counselling and advice on the risks of AEDs has formed part of formal NICE guidance since 2004 and at one time formed part of the Quality and Outcomes Framework, an incentive framework for GP practices.

Despite these steps – and many other awareness-raising measures - Epilepsy Action has repeatedly found, through a number of surveys, that women with epilepsy do not routinely receive pre-conception counselling and that many are not aware of the risks associated with sodium valproate and pregnancy. The latest figures from 2017 – 43 years after a link was mentioned in patient information leaflets – show that a fifth (21%) of respondents who take valproate had not had a discussion led by their healthcare professional to discuss risks around pregnancy and sodium valproate. 18% of women taking sodium valproate did not know about these risks. Together with the anecdotal evidence we are aware of, this demonstrates that some clinicians have not, and are still not, informing women of the risks or following the steps set out in NICE clinical guidance. It's unclear why this is, considering the potentially catastrophic consequences of women not being informed, and the fact that these risks have been widely agreed and accepted for several years.

Regulators like the MHRA have recently taken active steps to ensure women are aware of the risks and influence the prescribing rates for sodium valproate among women and girls of child bearing age. However, the MHRA's work has only begun to gain momentum in the last five years. Only very recently has it become mandatory for health professionals to discuss the issues with women before they can be prescribed sodium valproate, it would also be considered good clinical practice for the clinician to record the issues discussed in the clinical notes. Again it is unclear why steps were not taken sooner, given the body of evidence that exists. It is too early to know if the introduction of a mandatory action on this issue will improve awareness among women and decrease prescribing rates of valproate within this population.

It is unclear from the evidence if the manufacturers of sodium valproate should or could have done more to make women aware. While teratogenicity associated with sodium valproate has been included in patient information leaflets since its launch, more visible warnings, such as on the box itself, have only very recently been adopted.

Epilepsy Action believes that the incidence of harm to children born to women taking sodium valproate has occurred due to a combination of factors:

1. The decision by regulators, the Committee on Safety of Medicines, not to include information for patients about the risks when sodium valproate was first launched in 1973. This is despite health professionals being told at the time to only use sodium valproate in severe cases or when there was no alternative, and that the 'compound has been shown to be teratogenic in animals, meaning it could harm the human foetus.'
2. The lack of recognition by regulators, including the MHRA and its predecessors about the growing body of evidence about the impact of sodium valproate and their failure to take sufficiently robust action to ensure clinicians were aware of and responded to the risks. Further, for not ensuring the product manufacturers did more to ensure this information was clearly and prominently communicated to women taking sodium valproate.
3. The failure of many clinicians at both primary and secondary care level to follow the warnings in sodium valproate summary of product characteristics (SPCs) and ensure discussions with women of child bearing age took place to enable them to make informed decisions.
4. The failure from 2004 of many clinicians at both primary and secondary care level to follow NICE technology epilepsy appraisals, clinical guidelines and many other publications that clearly provided best practice guidance on sodium valproate and pre-conception counselling.
5. The failure of the government or medical regulators or colleges to implement any mechanism to ensure that NICE guidelines are followed consistently by clinicians, especially where there are clear safety implications within the guidance.
6. While complimenting the Quality and Outcomes framework for introducing an indicator for pre-conception counselling in 2011, the failure to do this earlier and the subsequent retirement of the indicator in 2014 have both exacerbated the issue. Further the failure by the bodies responsible for this decision to consult on the retirement (when the evidence of the impact of sodium valproate was growing even stronger) and the failure to ensure any mechanism for the continuation of pre-conception counselling meant opportunities to improve the situation were lost.

**Epilepsy Action welcomes any opportunity to be involved in further consultation or discussion on these issues. Epilepsy Action can provide copies of any of its advice and information materials mentioned in this submission.**

## **Background**

### **About Epilepsy Action**

Epilepsy Action is a community of people committed to a better life for everyone affected by epilepsy. As a member-led charity, we are led by and represent people with epilepsy, their friends, families and healthcare professionals. We're united in our demand for high quality, accessible epilepsy healthcare services, so that more people get the support they need to manage their condition. We want more people to understand the challenges of life with epilepsy, so that more people living with the condition are treated with fairness and respect. Together we provide support and expert advice so that fewer people are isolated by their epilepsy, and more can look forward to a life free from seizures.

### **Epilepsy and sodium valproate**

Valproate is a very effective epilepsy medicine for many people with epilepsy. However, the drug brings a risk of birth defects and development disorders in babies born to mothers taking this medication. Strong clinical evidence of the teratogenic effects of sodium valproate exists and the risk is high when compared to other epilepsy medicines or to women not taking epilepsy medication and the risk appears higher again if valproate is taken in combination with other epilepsy medicines. The link between sodium valproate and birth defects have been known for many years (see timelines attached with this submission), with guidance and warnings strengthening over time in light of the increasing evidence base.

There are no concrete figures to identify how many babies each year are affected by sodium valproate. Data is poorly captured and developmental abnormalities – and their link to valproate - are not always identified until children are older. One estimate suggests that 20,000 babies have been affected by sodium valproate in total and that around 400 babies a year are born to women taking sodium valproate.

Figures from the Medicines and Healthcare products Regulatory Agency (MHRA) suggest that up to four in 10 babies are at risk of developmental disorders if valproate is taken in pregnancy. The MHRA figures estimate that approximately one in 10 babies is at risk of physical birth defects. Babies affected by sodium valproate can have severe problems that require lifelong care and support.

### **Call for evidence**

Epilepsy Action has long believed that a clinician-led discussion about the risks, before a woman becomes pregnant – pre-conception counselling - is vital to try and avoid risk. This ensures that women are able to make an informed choice about those risks, in order to limit the number of babies being put at risk of birth defects and lifelong developmental problems.

It is clear from the series of surveys Epilepsy Action has undertaken over the years and the number of children still reported as being born with foetal, anticonvulsant syndrome, that too many women are still unaware of the risks of taking valproate in pregnancy. Epilepsy Action has been campaigning for many years (timeline of activity attached with this submission) for women and health professionals to be made more aware of the issues relating to epilepsy medicines, in particular those linked to pregnancy and sodium valproate.

It remains absolutely crucial that health professionals discuss the issues with relevant women and that they ensure women have a clear understanding of the risks linked to sodium valproate, and any associated impact on their epilepsy (i.e. the need to balance the mother's health and the need for seizure control, with the health of any unborn children).

We are aware of many women who had no knowledge of the risks associated with sodium valproate and whose children have been directly affected. Many started families well after the risks associated with sodium valproate were widely known and accepted by researchers, healthcare professionals and policy makers, yet they remained uninformed. Epilepsy Action supports calls for government to consider a financial support mechanism for those affected.

### **UK Epilepsy and Pregnancy register**

The UK Epilepsy and Pregnancy register, established in 1996, collects information about babies born to women with epilepsy and the frequency of malformations in babies exposed to anti-epileptic medication (AEDs) during pregnancy. Figures issued by the register in 2002, published on Epilepsy Action's website at the time, showed that the risk of birth defects in children born to women taking sodium valproate was two to three times that of women taking other anti-epileptic drugs.

Partly in response, the Committee on Safety of Medicines issued a warning about sodium valproate in 2003. The committee advised that women of childbearing age should not be prescribed sodium valproate without specialist neurological advice and that women already taking sodium valproate who are likely to become pregnant should receive specialist advice.

### **Formal incentives and regulatory changes**

In 2002, Epilepsy Action (as part of the Joint Epilepsy Council) called for new National Institute for Health and Care Excellence (NICE) guidelines on epilepsy in adults to include the need to inform women with epilepsy about the risks associated with AEDs and pregnancy. The recommendation was included in the final guidance and its importance has been clearly stated in NICE guidance since then.

Alongside other agencies, Epilepsy Action successfully campaigned to get pre-conception counselling added to the NHS Quality and Outcomes Framework in 2011. Epilepsy Action and the All-Party Parliamentary Group on Epilepsy originally suggested such an intervention in its 2007 report, *Wasted Money, Wasted Lives*. Unfortunately, the QOF was later retired in 2014. At this time, there was little transparency on how the decision was reached or the estimated impact on patients.

While the QOF indicator was in place, a 2013 survey highlighted that around a third of women had still not received information about pregnancy and the associated issues. Following the retirement of QOF, this figure rose to almost half of women, suggesting that this sort of intervention does have a positive impact.

Epilepsy Action has asked NICE to reintroduce pre-conception counselling as a Quality Outcome Framework (QOF) indicator as part of its current review of the framework. This will bring a formal incentive for clinicians to discuss pregnancy and the potential problems, with all women of child bearing age, who are prescribed anti-epileptic medication.

Epilepsy Action has also worked, and continues to work, to influence decision makers and government on this issue. We have sat on several expert panels and were instrumental in

encouraging the UK Medicines & Healthcare products Regulatory Agency (MHRA) to take a closer look at the guidance around prescribing sodium valproate.

In 2013, the MHRA referred sodium valproate to the European Medicines Agency (EMA) for a review. Concerns were raised in response to new data around the teratogenic effects of sodium valproate and whether the risks and benefits of valproate meant market authorisation should be maintained, varied, suspended or withdrawn.

Partly anticipating the outcome of the EMA review, the MHRA met with various groups, including Epilepsy Action, and started work on guidance for patients and professionals. In October 2014 the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) recommended strengthening the restrictions on the use of valproate medicines. It concluded that valproate should still be available. This recommendation was made to the EU's Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for a final decision. The recommendation was approved by CMDh and instructions issued to national bodies – including the MHRA - and manufacturers to implement it.

In January 2015 the MHRA issued a letter to inform healthcare professionals and bodies of important new information and strengthened warnings related to safety of medicines related to valproate. This included links to the information materials. The MHRA continued meeting with us and other charities in 2015 to see what additional work could be done to raise awareness of the issues.

In October 2015 George Freeman MP, Minister for Life Sciences, chaired a round table meeting on sodium valproate in pregnancy. The purpose of that and subsequent meetings was to focus on the key actions necessary to ensure that UK prescribing was in line with the strengthened product information. These meetings continued until George Freeman moved post after the election.

The MHRA formalised its interaction with patient groups, healthcare representatives and other relevant bodies and created the Valproate Stakeholders Network. Epilepsy Action has been, and continues to be, an active member of the network. Through this we have worked with the MHRA, professional bodies and with other patient groups to raise more awareness of the issues around valproate, to develop strengthened warnings about valproate and to produce new resources for people with epilepsy and for clinicians.

In February 2016, the MHRA released a valproate 'toolkit' to help healthcare professionals talk to women with epilepsy about the risks during pregnancy. The toolkit includes a credit card-sized patient card to be issued by pharmacists, booklets for healthcare professionals and women taking sodium valproate, and a checklist of important discussion points.

In April 2016 Epilepsy Action, Epilepsy Society and Young Epilepsy collaborated to jointly develop and promote a survey of women with epilepsy to find out the levels of awareness among women with epilepsy of the issues around valproate and the new guidance. This was to establish benchmark data for the uptake of the MHRA's new information. The results were shared with the MHRA and were promoted publicly in October 2016, bringing mainstream media awareness to the issue.

In March 2017 the medicines regulator in France, referred valproate back to the EMA to consider the effectiveness of the previous guidance and consider further measures. This

referral led to a PRAC public hearing in September 2017. The announcement of the hearing prompted Epilepsy Action to work with the other charities to repeat the 2016 survey to assess if awareness among women with epilepsy had improved.

Epilepsy Action and Epilepsy Society collaborated on an application to present verbal evidence at the PRAC public hearing. The verbal evidence presented focused on the results of the 2017 survey (which highlighted many women were still not being made aware of the issues) and the need for a mandatory requirement for women of child bearing age taking sodium valproate to be provided with relevant information to enable them to make an informed choice. In addition, Epilepsy Action independently submitted its own written evidence to the PRAC.

In response to recommendations made by the PRAC, in April 2018 the MHRA changed the licence for valproate medicines in the UK. Sodium valproate must no longer be prescribed to women or girls of childbearing age unless they are on the pregnancy prevention programme (PPP).

As part of the PPP, the prescriber must make sure women understand the risk if they became pregnant while taking the medicine. They must also recognise the need to take contraception while on the medicine. A risk acknowledgement form must be completed and signed during a review that must take place at least once a year. The PPP is mandatory for all women or girls of child-bearing age, who are taking sodium valproate, though ultimate responsibility for the decision to prescribe it (or not) rests with the prescribing clinician. It is still too early to tell if the programme has been effective in ensuring more women know of the risks. We plan to repeat our survey again in summer 2019 to measure the effectiveness of the most recent interventions, including the PPP.

### **Raising awareness among women and healthcare professionals**

Epilepsy Action provides impartial, fully accredited, evidence-based advice and information around all aspects of living with epilepsy. All of our information is independently reviewed and regularly updated. We keep abreast of new research and findings to help us provide the best possible information to people with epilepsy, and update our information accordingly.

We openly discuss the risks of malformations and neurodevelopmental impairments when taking sodium valproate in pregnancy. Since at least 1999, we have had a range of information materials which focus solely on women with epilepsy and the specific challenges they face, as well as comprehensive information on our website about sodium valproate and pregnancy.

Epilepsy Action advice and information materials as early as 1987 (earlier reference materials are unavailable) referenced the risk of foetal abnormalities and the need for women with epilepsy to consult a doctor before becoming pregnant. Epilepsy Action and others from the epilepsy community produced an 'Action in Epilepsy' manifesto in 1994 for improving the healthcare of for people with epilepsy. The document outlined the need for pre-conception counselling. Our information was referenced in valproate patient information leaflets in 2001.

Epilepsy Action has collaborated with other agencies to create several resources which aim to inform health professionals inform women of the risks around sodium valproate and pregnancy. These include a GP toolkit, outlining guidance for primary care practitioners

when managing the care of women with epilepsy, and an epilepsy and pregnancy obstetrics resource pack, aimed at midwives and obstetric professionals. We have also provided guidance and expert input on a range of external publications and information materials, including guidance produced by The Royal Society of Medicine and the Royal College of Obstetrics and Gynaecology. Guidance has made references to the teratogenic effects of sodium valproate and the need for pre-conception counselling for women with epilepsy who are of child bearing age.

Epilepsy Action has run a series of public campaigns over several years aimed at reducing the risks to mother and baby during pregnancy, by raising awareness among women and health professionals, since at least 2002. Epilepsy Action's Mothers in mind: healthy births (2007 and 2008) underlined the critical need for health professionals to increase their knowledge of how to best manage the condition in women before, during and after pregnancy. Campaigns in 2011 and 2013 once again raised awareness of the issue among women of child bearing age and health professionals, through the development of resources, media campaigns and the charity's extensive communications channels.

Most recently, a 2017 survey (a collaboration between Epilepsy Action, Epilepsy Society and Young Epilepsy) of 2,000 women with epilepsy showed that almost 1 in 5 (18%) women currently taking sodium valproate did not know it can potentially harm the development and physical health of their unborn child should they become pregnant. These results were in spite of efforts by the MHRA to raise awareness of the issue among healthcare professionals and women with epilepsy.

Epilepsy Action recognises this enquiry is focusing on the teratogenic effects of sodium valproate and what lessons can be learnt. We feel it important to use this opportunity to highlight that sodium valproate is not the only teratogenic ant-epileptic drug. There is increasing evidence that topiramate, and possibly other AEDs, have teratogenic effects and the recommendations of this review need to ensure that these issues are picked up and effectively managed by clinicians, regulators, guideline producers and others.

## Epilepsy Action sodium valproate timeline of activity October 2018

NB. Epilepsy Action became the working name of the British Epilepsy Association 2002

<b>1984</b>	British Epilepsy Association's magazine <i>Epilepsy Now</i> ran an article about women with epilepsy, highlighting that 'pre-conception counselling is an important part of the medical management of women with epilepsy.'
<b>1987</b>	British Epilepsy Association's The Medical Management of Epilepsy information booklet outlined the need for women with epilepsy to consult a doctor before becoming pregnant
<b>1991</b>	A book, <i>The Management of Epilepsy in General Practice</i> (Chadwick et al), was published highlighting the teratogenic risks of sodium valproate and that women should be made aware of this
<b>1994</b>	<i>Action in Epilepsy</i> , a publication of consensus (including representatives from British Epilepsy Association) guidelines for the management of epilepsy is published, highlighting teratogenic risks of AEDs and that women should be made aware of this
<b>1999</b>	<p>As part of the 'We Can' awareness-raising campaign, British Epilepsy Association produced <i>Epilepsy Mine</i>, a booklet of women's personal experiences of living with epilepsy.</p> <p>British Epilepsy Association's information booklet <i>Epilepsy and women</i> highlighted the need for pre-conception counselling and the potential impact of AEDs on the unborn child.</p> <p>British Epilepsy Association published <i>Epilepsy care – making it happen: a tool kit for today</i>. The publication included a foreword from the then Under Secretary of State for Health, John Hutton MP, and was developed by an advisory board of experts, supported by Sanofi Synthelabo (manufacturers of Epilim). It included advice on the potential teratogenic risks of AEDs.</p> <p>A BBC2 documentary <i>Home Ground</i> was broadcast in June 1999 and included 'a look at how some women are not told that the drugs used to control epilepsy can cause birth defects.' This caused a large spike in calls to British Epilepsy Association's Epilepsy Helpline around these issues.</p>
<b>2000</b>	<p>Parliamentary questions were put to the secretary of state about sodium valproate and its side effects.</p> <p>10 March 2000 To ask the Secretary of State for Health (1) what assessment he has made of (a) the side-effects of the drug Epilim, (b) the circumstances in which it should not be prescribed to children, (c) the number of cases since 1995 in which children who have been given Epilim have developed (i) fits and (ii) other adverse reactions,</p>

	(d) the number of cases since 1995 where Epilim has been given to pregnant women and (e) the number of cases since 1995 of pregnant women who have been treated with Epilim and who have then given birth to babies with birth defects;
<b>2001</b>	British Epilepsy Association's <i>Get Ahead</i> campaign focused on teenage girls and the specific issues that can affect them
<b>2002</b>	The charity carried out its first survey, <i>Ideal World for Women</i> , specifically focused on women with epilepsy and the challenges they face Epilepsy Action, as part of the Joint Epilepsy Council, highlighted the issues of teratogenicity in its submission to NICE for the draft of <i>NICE epilepsy technology appraisals 76 and 79, newer drugs for epilepsy in adults and children</i> .
<b>2003</b>	Findings from Epilepsy Action's <i>Ideal World</i> survey were published in academic journal as <i>Understanding the information needs of women with epilepsy at different life stages: results of the 'Ideal World' survey P. Crawford &amp; S Hudson, Seizure 2003; 12: 502–507</i>  The survey showed that women were not receiving important information about their condition and possible adverse effects of treatment, which could have profound implications for their health and the health of their unborn child.  Epilepsy Action published the <i>Epilepsy Resource Pack</i> , an information booklet and toolkit aimed at primary care professionals. This was following the introduction of the Quality and Outcomes framework markers for epilepsy in the GMS contract. 10,000 paper copies were circulated to GP practices in England and 1,000 copies downloaded from Epilepsy Action's website. The executive summary highlighted the issue of teratogenicity as did a section addressing issues for women with epilepsy. The toolkit contained a template checklist for women of childbearing potential.  Epilepsy Action's advice and information publications <i>Women matter</i> and <i>Women</i> included advice on teratogenic risks and the need for pre-conception counselling.  Epilepsy Action conducted a media campaign to raise awareness of the <i>Women Matter</i> booklet and the issues it covered (supported by Glaxo Wellcome).
<b>2004</b>	Contraception Week featured a series of Epilepsy Action interviews to highlight the possible interaction between AEDs and contraception.  The <i>NICE technology appraisal 74, Newer drugs for epilepsy in adults</i> , was published in March containing the following guidance: "In women of childbearing potential, the possibility of interaction with oral contraceptives and the risk of the drugs causing harm to

	<p>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.”</p> <p>The <i>NICE technology appraisal 79, Newer drugs for epilepsy in children</i>, was published in April and contained the following guidance:      “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.”</p> <p>In October 2004 the NICE guidelines <i>The epilepsies The diagnosis and management of the epilepsies in adults and children in primary and secondary care</i>, CG20, was published.</p> <p>This included within the key priorities for implementation:      Special considerations for women of childbearing potential      “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.”</p> <p>In addition to including the guidance from the technology appraisal it included:      “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.”</p> <p>Appendix D to CG20 included a checklist for women, adopted from Epilepsy Action’s <i>Women with Epilepsy Checklist</i> which highlighted the need to discuss the teratogenic effect of AEDs.</p> <p>Epilepsy Action produced a leaflet for patients <i>The Epilepsies: You, epilepsy &amp; the NICE Guideline</i> which highlighted the risk that some AEDs can harm the unborn child.</p>
<b>2005</b>	<p>The new <i>National Service Framework on long-term conditions</i> set out 11 quality requirements to improve the care of all people living with a long-term condition. In addition, NICE and SIGN guidelines provided a structure for management of people with epilepsy,</p>

	<p>which includes addressing issues specific to women upon Epilepsy Action's recommendation</p>
<b>2006</b>	<p>In the spring, Epilepsy Action's campaign <i>Mothers in Mind</i> was launched, encompassing new evidence from the UK Pregnancy Register which showed 96% of babies born to women with epilepsy did not have any major congenital malformations (MCMs). The study showed that women still face a risk of having a baby with MCMs and less severe problems which can be related to having epilepsy and to taking AEDs</p> <p>The campaign highlighted the need for pre-conception counselling. Epilepsy Action members reported that many women are still not provided with this level of information or care</p> <p>As part of the campaign an information booklet was launched offering lay information on issues from contraception and planning a baby</p> <p>In the autumn Epilepsy Action launched <i>Lifeline – from adolescence to menopause</i>, a campaign highlighting the need for all healthcare professionals to be aware of the complex issues faced by women with epilepsy at different stages of their life (puberty, pregnancy, and menopause). The campaign includes a <i>Women and Epilepsy</i> booklet for healthcare professionals.</p> <p>Organisation for Anti-Convulsant Syndrome (OACS) and legal firm Irwin Mitchell brought a UK court action against Sanofi on behalf of 164 children whose mothers say they suffered birth defects because of sodium valproate. The case is publicly funded by legal aid through the Legal Services Commission (LSC). Epilepsy Action publicly offered supportive comments on the case, including in the national media. Six weeks before the trial was due to start the LSC announced it was withdrawing funding.</p>
<b>2007</b>	<p>An Epilepsy Action <i>Ideal World for Women</i> survey revealed that only 21% of women were receiving pre-conception counselling. 82% said that they were aware AEDs can cause birth defects. 63% had been given information on the affect an AED may have on an unborn child. 25% said they had not been given any information relating to pregnancy and AEDs</p> <p>Epilepsy Action suggested a new Quality and Outcomes Framework (QOF) indicator to ensure more women receive pre-conception counselling</p>
<b>2008</b>	<p>Epilepsy Action launched the <i>Mothers in Mind: Healthy Births campaign</i>, providing tools to help health professionals give better advice and care. Epilepsy Action continued to push for better access to pre-conception counselling</p> <p>Epilepsy Action launched a new online service <i>The Pregnancy Diaries</i></p>

	<p>The <i>Saving Mothers' Lives</i> report, which reviewed maternal deaths, was published in the British Journal of Obstetrics and Gynaecology, recommending greater provision of pre-conception advice</p> <p>New research <i>Autism Spectrum Disorders Following in Utero Exposure to Antiepileptic Drugs</i> was published in Neurology journal. It concluded that there is a link between the AED sodium valproate and having children on the ASD. According to the report women taking sodium valproate face a seven times greater risk.</p>
<b>2011/12</b>	<p>Pre-conception counselling indicator was added to the QOF providing an incentive to GPs, stating: 'Women taking AEDs receive vital pre-conception counselling.'</p> <p>Latest figures suggested an estimated 131,000 women with epilepsy of child-bearing age in the UK; 5000 of these become pregnant every year.</p>
<b>2012</b>	<p>Epilepsy Action repeated its <i>Ideal World for Women</i> survey</p> <p>51% of women had received information about contraception and epilepsy, 28% on conception and epilepsy, 46% on pregnancy and epilepsy and 36% had received information on none of these issues. 67% had discussed the potential risks associated with taking certain AEDs in pregnancy.</p>
<b>2013</b>	<p>Epilepsy Action strengthened its statement on sodium valproate to say the drug should not be a first-line treatment for women of child-bearing age</p> <p>Epilepsy Action launched its <i>HealthE mum-to-be</i> campaign, including a media campaign. The <i>Pregnancy Diaries</i> magazine was created, including the story of a family affected by foetal anti-convulsant syndrome</p> <p>An <i>Epilepsy in pregnancy obstetrics resource pack</i> is produced with a group of epilepsy specialists to help health professionals give the best advice and care to women with epilepsy</p> <p>A Medicines &amp; Healthcare products Regulatory Agency (MHRA) 'Drug Safety Update' bulletin (volume 7 issue 4) reminded "healthcare professionals that sodium valproate should not be used during pregnancy and in women of child bearing potential unless clearly necessary."</p> <p>The MHRA referred sodium valproate to the European Medicines Agency (EMA) for a review, raising concerns about the new data around teratogenic effects of sodium valproate and whether the risks and benefits of valproate mean market authorisation should be maintained, varied, suspended or withdrawn.</p>

<p><b>2014</b></p>	<p>Retirement of QOF indicator EP003 'The percentage of women aged 18 or over and who have not attained the age of 55 who are taking AEDs who have a record of information and counselling about contraception, conception and pregnancy in the preceding 12 months.'</p> <p>Epilepsy Action campaigned against this, including meeting with Dr Chaand Nagpaul, Chair of the BMA General Practitioners Committee in January 2014. At this meeting the BMA assured us that GPs would still meet the QOF requirements, despite evidence presented to them that in fact many GPs were failing to meet the requirements and adhere to the strengthened MHRA advice. Of concern at the time was that the retirement of the indicator contradicted the advice of the NICE QOF advisory committee who advised that the indicator should be retained (with amendment). At no point were patient groups consulted on the proposed retirement.</p> <p>Partly anticipating the outcome of the EMA review, the MHRA met with various groups, including Epilepsy Action, and started work on guidance for patients and professionals.</p> <p>The EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb. It concluded that valproate should still be available.</p> <p>The recommendation was approved and instructions were issued to national bodies (the MHRA in the UK) and manufacturers to implement it.</p>
<p><b>2015</b></p>	<p>The MHRA strengthened warnings on the risks of valproate in pregnancy after pressure from Epilepsy Action</p> <p>MHRA worked with stakeholders, including Epilepsy Action,, to produce a toolkit</p> <p>George Freeman MP, Minister for Life Sciences, chaired a round table meeting on sodium valproate in pregnancy. (These meetings continued until George Freeman moved post the following year)</p> <p>MHRA formalised input of other agencies and groups with the creation of the Valproate Stakeholder Network, of which Epilepsy Action continues to be an active member.</p> <p>Epilepsy Action input into new RCOG guidance on Epilepsy in Pregnancy asking for additions relating to sodium valproate.</p>

<p><b>2016</b></p>	<p>MHRA launched a new toolkit to ensure women are better informed of taking valproate medicines in pregnancy</p> <p>A survey developed by Epilepsy Action, Epilepsy Society and Young Epilepsy found that only 20% of women taking sodium valproate know the risks, 20% of women taking sodium valproate did not know the risks and 27% of those taking sodium valproate had not had a discussion about pregnancy with a healthcare professional.</p> <p>French government agreed to set aside a compensation fund for families affected by sodium valproate in France</p>
<p><b>2017</b></p>	<p>The medicines regulator in France referred valproate back to the EMA to consider the effectiveness of the previous guidance and consider further measures.</p> <p>This referral led to a Pharmacovigilance Risk Assessment Committee (PRAC) public hearing in September 2017. Epilepsy Action submitted written evidence and presented oral evidence jointly with Epilepsy Society.</p>
<p><b>2018</b></p>	<p>In response to the recommendations made by the PRAC, in April 2018 the MHRA changed the licence for valproate medicines in the UK. Sodium valproate must no longer be prescribed to women or girls of childbearing age unless they are on the pregnancy prevention programme (PPP).</p> <p>The MHRA and members have the valproate stakeholder network are working to make sure all relevant groups are aware of, and acting upon, the stipulations of the pregnancy prevention programme,</p>

**Timeline of Patient Information Leaflets (PIL) and Summary of Product Characteristics (SPC) related to teratogenicity of sodium valproate  
October 2018**

<p><b>1974</b> <b>1975</b> <b>1978</b> <b>1979</b> <b>1980</b> <b>1981</b></p>	<p><u>Reckitt-Labaz, Epilim datasheets.</u></p> <p>“contra-indications, warnings, etc” section contained specific reference to “precautions- women of childbearing age”</p> <p>Recognition of demonstrated teratogenic properties in laboratory experiments in animals. Notes that in women of childbearing age, the benefits of its use should be weighed against the possible hazard suggested by these findings.</p>
<p><b>1993</b></p>	<p><u>Epilim, Summary of Product Characteristics (SPC)</u></p> <p>“Treatment of generalised, partial or other epilepsy in women of childbearing age valproate should only be used in severe cases or in those [missing word, assumed to be ‘resistant’] to other treatment”</p>
<p><b>1996</b></p>	<p><u>Epilim, Summary of Product Characteristics (SPC)</u></p> <p>“4.1 Therapeutic Indications - In the treatment of generalised, partial or other epilepsy. In women of child bearing age, Epilim should be used only in severe cases or those resistant to other treatment.”</p> <p>“4.6 Pregnancy and Lactation - An increased incidence of congenital abnormalities (including facial dysmorphism, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.</p> <p>The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.</p> <p>The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alphafoetoprotein measurement, ultrasound and other techniques if appropriate.”</p>

1997

Epilim, Patient Information Leaflet (PIL)

“Epilim Chrono and Pregnancy – It is known that women who have epilepsy have a slightly higher risk of having a child with an abnormality than other women. Women who have to take Epilim during the first 3 months of pregnancy to control their epilepsy have about a 1-2% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. **There may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy.** It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.”

Epilim, Summary of Product Characteristics (SPC)

*Relevant additional information included in this version*

“4.1 Therapeutic Indications - In the treatment of generalised, partial or other epilepsy. In women of child bearing age, Epilim should be used only in severe cases or those resistant to other treatment.

4.6 Pregnancy and Lactation - An increased incidence of congenital abnormalities (including facial dysmorphism, neural tube defects and multiple malformations particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alphafoetoprotein measurement, ultrasound and other techniques if appropriate.

	<p>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbital and other enzyme-inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.”</p>
<p><b>2001</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p> <p>Reference to British Epilepsy Association (Epilepsy Action) support services</p> <p>“the British Epilepsy Association (telephone: 0808 800 5050) will also be happy to try and answer any general questions on epilepsy”</p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u>  <i>Relevant additional information included in this version</i></p> <p>Notable that the warning previously included at the start of the SPC, 4.1 Therapeutic Indications, as included above is not similarly present in the 2001 SPC. First mention of risk is on page 3, 5<sup>th</sup> item in the list.</p> <p>Inclusion of risks during pregnancy in ‘Special Warnings’ section.</p> <p>“4.4. Special Warnings and Precautions for Use – Pregnancy”</p>
<p><b>2003</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p> <p>Specific mention of the need to discuss potential pregnancy with a medical professional or alert them immediately if you become pregnant.</p> <p>“Pregnancy – Ask your doctor or pharmacist for advice before taking any medicine. It is essential that you discuss your epilepsy treatment with your doctor well before you become pregnant. If at any time you suspect that you might already be pregnant you must be tell your doctor immediately.”</p> <p>Specific reference to other birth defects.</p> <p>“There is also an increased risk of other birth defects.”</p>

Specific reference to developmental delay.

“Infants born to mothers who took Epilim during pregnancy may develop less quickly than normal. This may also be because of the mother’s epilepsy but the exact cause is unknown.”

Epilim, Summary of Product Characteristics (SPC)

*Relevant additional information included in this version*

Language around women of childbearing age being prescribed Epilim is significantly stronger. Specific reference to seeking specialist advice in light of potential teratogenic risk.

“4.4. Special Warnings and Special Precautions for Use - Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).”

Substantial additional information provided in 4.6, Pregnancy and Lactation.

“4.6. Pregnancy and Lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

*- Risk associated with epilepsy and antiepileptics*

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of

these or of maternal antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

*- Risk associated with valproate*

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphism, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate. Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

*- In view of the above data*

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000 mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully

	<p>screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).”</p>
<b>2004</b>	<p><u>Epilim, Patient Information Leaflet (PIL)</u></p> <p>No changes to 2003 Epilim PIL as set out above.</p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u></p> <p>4.42 Precautions – Pregnancy. No changes to 2003 Epilim SPC as set out above.</p> <p>4.6 Pregnancy and Lactation – No changes to 2003 Epilim SPC as set out above.</p> <p>“4.8 Undesirable Effects - Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and Lactation)”</p>
<b>2008</b>	<p><u>Epilim, Summary of Product Characteristics (SPC)</u> <i>Relevant additional information included in this version</i></p> <p>Specific reference to counselling services for all women with epilepsy of childbearing age.</p> <p>“4.4 Special warnings and precautions for use - Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).”</p>
<b>2010</b>	<p><u>Epilim, Patient Information Leaflet (PIL)</u> <i>Relevant additional information included in this version</i></p> <p>Notably stronger language used in 2010 PIL.</p> <p>“Pregnancy and breast-feeding</p> <p>Women who could become pregnant</p> <p>Before you start taking Epilim Chrono, your doctor should discuss with you the possible problems when it is taken in pregnancy.</p> <ul style="list-style-type: none"> <li>• Unplanned pregnancy is not desirable in women taking Epilim Chrono</li> <li>• <b>You should use an effective method of contraception and talk to your doctor before planning pregnancy.</b> Epilim Chrono has no effect on how well the oral contraceptive pill works.</li> </ul>

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.”

Inclusion of a comprehensive list of possible childhood abnormalities.

“Women taking Epilim during pregnancy have a higher risk than other women of having a child with an abnormality. The chance of abnormalities is increased if you are also taking other medicines for epilepsy at the same time. These abnormalities include:

- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations with heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called ‘Spina bifida’”

Specific reference to autistic disorders.

“Some babies born to mothers who took Epilim Chrono during pregnancy may develop less quickly than normal or have autistic disorders. These children may require additional educational support.”

Notably stronger language used in 2010 PIL.

“Women who are planning to get Pregnant

If you become pregnant, think you may be pregnant or plan to become pregnant while taking Epilim Chrono, you must tell your doctor straight away.

- Your doctor will give you appropriate counselling and will suggest changes to your treatment or dose
- He or she will also want to check your progress while you are pregnant

It is very important that you discuss your treatment with your doctor well before you become pregnant.”

Epilim, Summary of Product Characteristics (SPC)

*Relevant additional information included in this version*

“4.4.1 Special warnings... Women of childbearing potential (see section 4.6):

A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital

anomalies to the unborn child. This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation).”

Inclusion of additional data to demonstrate the prevalence and type of possible birth abnormalities.

“Risk associated with valproate

...

Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.

Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy.”

<p><b>2011</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p> <p>Stronger language made more prominent through formatting.</p> <p><b>“Pregnancy and breast-feeding  Women who could become pregnant you should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor.”</b></p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u>  <i>Relevant additional information included in this version</i></p> <p>Stronger language again.</p> <p>“4.6.1 Pregnancy  ...  - In view of the above data  The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy.</p> <p>If a women plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication”</p>
<p><b>2012</b></p>	<p><u>Depakote, Patient Information Leaflet (PIL) – Valproic Acid, not Sodium Vaploate</u></p> <p>No substantive changes to Epilim PIL as set out above.</p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u>  <i>Relevant additional information included in this version</i></p> <p>No substantive changes to Epilim SPC as set out above.</p>
<p><b>2014</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p>

	<p>No substantive changes to Epilim PIL as set out above.</p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u>  <i>Relevant additional information included in this version</i></p> <p>Substantial additional evidence included.</p> <p>“4.6.1 Pregnancy</p> <p>Data from a meta-analysis (including registries and cohort studies) has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy at 10.73% (95% CI: 8.16 – 13.29). Available data indicate dose dependency of this effect. Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.”</p>
<p><b>2015</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p> <p>Substantial update to the PIL including additional evidence, stronger language and situational breakdown of advice.</p> <p><b>“Pregnancy and breast-feeding  Important advice for women</b></p> <ul style="list-style-type: none"> <li>• Valproate can be harmful to unborn children when taken by a woman during pregnancy.</li> <li>• Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.</li> <li>• It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.</li> <li>• 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.</li> <li>• 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</li> </ul>

walk and talk, intellectually less able than other children, and have difficulty with language and memory.

- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

#### **FIRST PRESCRIPTION**

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

#### **Key messages:**

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

#### **CONTINUING TREATMENT AND NOT TRYING FOR A BABY**

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

#### **Key messages:**

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

#### **CONTINUING TREATMENT AND CONSIDERING TRYING**

#### **FOR A BABY**

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any

risks to you and your unborn child are reduced as much as possible. Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby.

Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

**Key messages:**

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy is controlled and the risks to your baby are reduced
- Tell your doctor at once when you know or think you might be pregnant.

**UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT**

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once.

Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

**Key messages:**

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

**Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.”**

Epilim, Summary of Product Characteristics (SPC)

*Relevant additional information included in this version*

Substantial revisions made to Epilim SPC.

**“4.4.1 Special Warnings - Female children/Female adolescents/Women of childbearing potential/Pregnancy:**

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders

in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy (see section 4.6).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.”

More detail and evidence to support concerns previously raised, explicit acknowledgement that risk of intellectual impairment may be independent from maternal IQ. Explicit reference to ADHD.

#### **“4.6 Fertility, pregnancy and lactation**

...

##### *Developmental disorders*

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.

	<p>Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).”</p>
<p><b>2016</b></p>	<p><u>Epilim, Patient Information Leaflet (PIL)</u>  <i>Relevant additional information included in this version</i></p> <p>First time a standalone warning box has been included in the PIL. This warning box is situated on the front page and clearly delineated, the first time that warnings about teratogenicity have been included on the front of the PIL.</p> <p>“This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects</p> <p style="text-align: center;"><b>WARNING</b></p> <p>Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment. Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant”</p> <p><u>Epilim, Summary of Product Characteristics (SPC)</u>  <i>Relevant additional information included in this version</i></p> <p>“ ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.”</p>

**Scientific research on sodium valproate in pregnancy timeline of activity  
October 2018**

<p><b>1976</b></p>	<p>Whittle BA. <i>Preclinical teratological studies on sodium valproate (Epilim) and other anticonvulsants</i>. In: Legg NJ, ed. <i>Clinical and pharmacological aspects of sodium valproate (Epilim) in the treatment of epilepsy Tunbridge Wells: MCS Consultants, 1976: 105-10.</i></p> <p>Demonstrated the teratogenicity of sodium valproate in rabbits, rats and mice when given in large doses</p>
<p><b>1980</b></p>	<p>Brown NA, Kao J, Fabro S. <i>Teratogenic potential of valproic acid. Lancer 1980; i: 660-61</i></p> <p>Demonstrated the teratogenicity of sodium valproate in rabbits, rats and mice when given in large doses</p>
<p><b>1982</b></p>	<p><i>'Valproate and Malformations'</i>The Lancet, December 1982, 1313-1314  <a href="https://www.sciencedirect.com/science/article/pii/S014067368291515X">https://www.sciencedirect.com/science/article/pii/S014067368291515X</a></p> <p>“Published case reports of congenital defects in infants exposed to valproate in utero include the following: craniofacial and thoracic-cage anomalies associated with dislocated hip and bundle branch block, lumbosacral spina bifida with hydrocephalus (exposure also to clonazepam and phenobarbitone); Fallot’s tetralogy, alveolar cleft, and hypoplastic nails (exposure also to carbamazepine and primidone); dysmorphic face, hypoplastic digits, and possible ventricular septal defect. Nau et al.’ described 12 infants exposed to valproate, several of whom had diastasis recti abdominis, hernias, nail hypoplasia, and minor facial anomalies. One had a ventricular septal defect and another patent ductus arteriosus.</p> <p>The Lancet has been shown data from reports to the manufacturers concerning pregnancy outcomes after valproate. These are inevitably non-representative; nevertheless, the kinds of malformations reported are of interest. In ninety-eight reports, 19 pregnancies were abnormal; spina bifida was recorded in 7 pregnancies (2 of which were terminated), but there were no cases of anencephaly. 5 of the mothers had taken anticonvulsants additional to valproate. Of 6 infants with multiple defects not involving the central nervous system, 4 had cardiac lesions. Another infant had isolated congenital heart disease. Jeavons 15 has analysed both published and unpublished data.”</p> <p>“Urgent action is needed on several fronts. Confirmation of the suggested association should be sought from other birth defects registries such as those collaborating under E.E.C. auspices in a Concerted Action Project. Trends in spina bifida prevalence should be related to sales of valproate. Of particular relevance are sales data in the Rhone-Alpes region. Did they rocket in 1980? Is the teratogenic mechanism in animals understood and can this be studied in nonpregnant human beings?</p> <p>Until this matter is resolved, clinicians must deal with two practical problems. The first is the management of epilepsy in pregnancy. The</p>

	<p>manufacturer's data sheet for 'Epilim' (sodium valproate) in the U.K. states clearly that the drug is teratogenic in animals and advises, "In women of child-bearing age, the benefits ... should be weighed against the possible hazard suggested by these findings". This applies to other anticonvulsants, and the relative teratogenic risks of different drugs are not accurately known. Good control of seizures in pregnancy is desirable, and decisions on therapy must rest on clinical judgment. The second problem is raised by the final sentence of the Clearinghouse letter, "We believe that women who have been exposed to valproic acid in the first trimester should be informed of the risk and offered counselling". Since the risk reported relates exclusively to open spina bifida, such women might reasonably be offered amniocentesis."</p>
<p><b>1990</b></p>	<p>Yerby, M. S &amp; Leppik, I 'Epilepsy and the outcomes of pregnancy'  <a href="https://www.sciencedirect.com/science/article/pii/0896697490900462">https://www.sciencedirect.com/science/article/pii/0896697490900462</a></p> <p>"No anticonvulsant drug can be considered absolutely safe in pregnancy, yet most of these drugs have not been associated with any specific pattern of major malformations .The exception is valproic acid, which has been associated with a 1-1 1/2% rate of spina bifida .This represents a 20-fold increase risk compared to the rate in the general population (21)."</p> <p>...</p> <p>"Women of child-bearing age with epilepsy need to be informed of the risks of pregnancy associated with anticonvulsant use prior to conception if at all possible (Table 4).They also need to know that seizures can be harmful to mother and fetus and that risks can be reduced with proper care "</p>
<p><b>1999</b></p>	<p>Crawford, P &amp; Lee, P 'Gender difference in management of epilepsy—what women are hearing' <i>Seizure</i> 1999; 8: 135–139</p> <p>A study of the results of a British Epilepsy Association (BEA) survey of 1855 female members.</p> <p>"The women were asked about the advice they had received about pregnancy (Table 9). Six hundred and thirty-seven (34 %) claimed they had not received any advice and 459 (25 %) had not discussed pregnancy with anyone. Amongst those who had already had children, 232 (38 %) claimed not to have received any advice about pregnancy and epilepsy and only 210 (24 %) had discussed the issues with a doctor before conception."</p> <p>"One of the more important issues is that of antiepileptic drug therapy. The risk of foetal malformation is increased if a woman is on polytherapy, particularly if sodium valproate is part of the combination.  ...Very few of the women respondents were aware of the need to take folic acid before, and for the first 3 months after conception. Over half the women who returned the questionnaire felt that they had not been provided with enough information about pregnancy; in particular, few had received information about teratogenicity of antiepileptic drugs or the need for pre-conception counselling"</p>

<p><b>2000</b></p>	<p><i>Fairgrieve, S. D et al. 'Population based, prospective study of the care of women with epilepsy in pregnancy' BMJ 2000;321:674-5</i></p> <p>"The study shows that guidelines in the literature for the management of women with epilepsy are not being followed.<sup>3 4</sup> Most women with epilepsy in our region are supervised by their general practitioner, control of seizures is poor, compliance with medication is variable, and methods of preconceptional counselling are ineffective. ... Considerable expansion of epilepsy services in primary and secondary care is needed if the guideline recommendations<sup>3 4</sup> are to be achieved.<sup>5</sup>"</p>
<p><b>2002</b></p>	<p><i>Mawer, G. Clayton-Smith, J. Coyle, H &amp; Kini, U. 'Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate'</i>  <a href="https://www.sciencedirect.com/science/article/pii/S1059131102001358">https://www.sciencedirect.com/science/article/pii/S1059131102001358</a></p> <p>"Despite its limitations the results of this study add to the growing body of evidence that VPS in pregnancy at doses above 1000 mg per day carries a particular risk of adverse outcome. Sodium valproate at such doses should therefore be avoided when pregnancy is likely."</p>
<p><b>2003</b></p>	<p><i>Crawford, P &amp; Hudson, S 'Understanding the information needs of women with epilepsy at different lifestages: results of the 'Ideal World' survey' Seizure 2003; 12: 502-507</i></p> <p>"The survey reveals that women with epilepsy are not receiving important information regarding treatment and its possible adverse effects, which could have profound implications for their health and the health of their unborn child. Previous studies suggest that women with epilepsy are unlikely to proactively seek a review of their treatment. To improve the current situation, all women with epilepsy of childbearing age should be offered a review, initially in general practice, to ensure that appropriate treatment changes can be made in a timely fashion. Thereafter, regular review and discussion should be encouraged to discuss treatment and stage of life issues."</p>
<p><b>2004</b></p>	<p><i>Vada, FJ et al. 'Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy'</i>  <a href="https://www.sciencedirect.com/science/article/pii/S0967586804001572">https://www.sciencedirect.com/science/article/pii/S0967586804001572</a></p> <p>"Conclusions. There is a dose-effect relationship for FM and exposure to VPA during the first trimester of pregnancy, with higher doses of VPA associated with a significantly greater risk than with lower doses or with other AEDs. These results highlight the need to limit, where possible, the dose of VPA in pregnancy."</p> <p><i>Adab, N et al. 'The longer term outcome of children born to mothers with epilepsy'</i>  <a href="https://jnnp.bmj.com/content/75/11/1575">https://jnnp.bmj.com/content/75/11/1575</a></p> <p>"Results: A total of 249 children aged 6 and over were studied: 41 were exposed to sodium valproate, 52 to carbamazepine, 21 to phenytoin, 49 to polytherapy, and 80 were unexposed. Mean verbal IQ was significantly lower in the valproate group compared to unexposed and other monotherapy</p>

	<p>groups. Multiple regression analysis showed that both valproate exposure and frequent tonic-clonic seizures in pregnancy were significantly associated with a lower verbal IQ despite adjusting for other confounding factors. There was a significant negative correlation between dysmorphic features and verbal IQ in children exposed to valproate.</p> <p>Conclusions: This study identifies valproate as a drug carrying potential risks for developmental delay and cognitive impairment and is the first to suggest that frequent tonic-clonic seizures have a similar effect. Our results need to be interpreted with caution given their retrospective nature. Women with epilepsy need careful counselling about individual risk benefit of AED treatment before pregnancy.</p> <p>...</p> <p>The results of our study are of concern given that valproate was first licensed in the United Kingdom in 1975. The last 10 years have seen the licensing of seven new AEDs, some of which may come to be used commonly during the childbearing years. It is essential that adequately controlled prospective studies are established now to identify the level of risk for cognitive impairment in children of women taking both new and established AEDs during pregnancy.</p> <p>Our data demand that epilepsy services deliver adequate information and counselling about drug treatment during childbearing years. This needs to be offered before pregnancy and updated regularly. Counselling might initially take place as part of an adolescent clinic transferring care from paediatric to adult services. Current services and practice would need to evolve considerably as for many women these issues are only raised when they present in the first trimester of pregnancy.”</p>
<p><b>2005</b></p>	<p><i>Morrow, J et al. 'Malformation risks of anti-epileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register.'</i>  <a href="https://jnnp.bmj.com/content/jnnp/early/2005/09/12/jnnp.2005.074203.full.pdf">https://jnnp.bmj.com/content/jnnp/early/2005/09/12/jnnp.2005.074203.full.pdf</a></p> <p>“Only 4.2% of live births to women with epilepsy had an MCM. The MCM rate for polytherapy exposure was greater than for monotherapy exposure. Polytherapy regimens containing valproate had significantly more MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM.</p> <p>...</p> <p>However, infants exposed to more than 1000mg of valproate had the highest MCM rate for any monotherapy exposure at 9.1%.”</p>
<p><b>2006</b></p>	<p><i>Meador, K. J et al. 'In utero antiepileptic drug exposure: Fetal death and malformations' Neurology: 2006: 67: 407-412</i></p> <p>“More adverse outcomes were observed in pregnancies with in utero valproate exposure vs the other antiepileptic drugs (AEDs). These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus. For women who fail other AEDs and require valproate, the dose should be limited if possible.</p> <p>...</p>

	<p>VPA poses a higher risk of anatomic teratogenesis than other commonly used AEDs. The current data suggest an increased risk of behavioral teratogenesis for VPA, but additional studies are needed to confirm this risk separately. Nevertheless, the overall increased risk of poor outcomes for VPA is clear. Clinicians should consider this risk in the choice of AED for women and should specifically advise their female patients of this risk. Although VPA will continue to be an important treatment option in women who fail other AEDs, we advise that VPA not be used as the AED of first choice for women of child-bearing potential, and, when used, its dose should be limited, if possible.”</p>
<b>2008</b>	<p><i>Bromley, R. Mawer, G &amp; Baker, G. A. ‘Autism spectrum disorders following in utero exposure to antiepileptic drugs.’</i>  <a href="https://www.ncbi.nlm.nih.gov/pubmed/19047565">https://www.ncbi.nlm.nih.gov/pubmed/19047565</a></p> <p>“The finding that 6.3% of the children exposed to monotherapy VPA in utero have ASD or features of this disorder is seven times higher than the control group (0.9%) and higher than the reported incidence of 6 per 1000 children in the general population<sup>7</sup>. It is therefore concluded that exposure to VPA in utero carries an increased risk for the development of ASD. Women who are prescribed VPA during pregnancy should be counseled preconceptually and informed specifically on this risk.”</p>
<b>2009</b>	<p><i>Bromley, R. Baker, G &amp; Meador, K. J ‘Cognitive abilities and behaviour of children exposed to antiepileptic drugs in utero’</i>  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743524/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743524/</a></p> <p>“There is an accumulating body of evidence that children exposed to VPA in utero are at an increased risk of cognitive impairment at a young age and that exposure poses an increased risk for the later development of ASD.  ...  The accumulating body of evidence clearly identifies that exposure to AEDs <i>in utero</i> carries a risk of cognitive and behavioural problems. It is clear that more research is needed in order to allow comprehensive preconceptual advice to be given to women with epilepsy who are planning a pregnancy.”</p>
<b>2013</b>	<p><i>Meador, K. J et al ‘Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study’</i>  <a href="https://www.thelancet.com/journals/lanneur/article/PIIS1474-4422(12)70323-X/fulltext">https://www.thelancet.com/journals/lanneur/article/PIIS1474-4422(12)70323-X/fulltext</a></p> <p>“Similar to our findings in children aged 3 years and 4·5 years, 3,16 children with fetal exposure to valproate had reduced IQ (7–10 points) at 6 years compared with other commonly used antiepileptic drugs (ie, carbamazepine, lamotrigine, and phenytoin). Valproate exposure was also associated with worse verbal and memory abilities compared with the other antiepileptic drugs, and worsened non-verbal and executive functions compared with lamotrigine. Teratogens act in a dose-dependent manner and according to genetic susceptibility. An increased valproate dose was associated with</p>

	reduced IQ, verbal, non-verbal, memory, and executive function, but other antiepileptic drugs had no dose effects. Thus, fetal exposure to valproate is associated with a range of cognitive deficits.”
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