

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

## **Written Evidence**

### **Manufacturers of Sodium Valproate**

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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.**



**SANOFI**

**SANOFI SUBMISSION TO INDEPENDENT MEDICINES &  
MEDICAL DEVICES SAFETY REVIEW CALL FOR EVIDENCE**

**Reference: AZNFVK**

**October 2018**



Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence. Reference: AZNFVK. Oct 18

## **SUMMARY**

- Valproate is an essential medicine as defined by the WHO.
- Sanofi has communicated the risk associated with valproate, as approved by regulatory authorities, consistent with the medical and scientific knowledge available at the time.
- Sanofi works under the supervision of regulators so that the risks associated with valproate use during pregnancy are appropriately communicated to patients, doctors and pharmacists.
- Sanofi is keen to engage with this review to provide information and our perspective on valproate.

## **BACKGROUND**

### **Epilepsy:**

- There are around 60 different types of seizure<sup>i</sup> and more than 20 different anti-epileptic medicines are available<sup>ii</sup>.
- Despite this, approximately 30% of patients with epilepsy do not have their seizures fully controlled and around 1,000 people with epilepsy die prematurely in the UK each year<sup>iii</sup>.
- Approximately 600,000 people in the UK have a diagnosis of epilepsy and take anti-epileptic medication. Around 77% of these people are men or women who are not of child-bearing age (12 -50 years)<sup>iv</sup>.

### **Bipolar:**

- Bipolar is a common life-long mental health disorder. Worldwide prevalence rates are estimated to be between 1% and 5% depending on the part of the bipolar spectrum assessed and the instruments used<sup>v</sup>. The 2014 Adult Psychiatric Morbidity Survey<sup>vi</sup> found that 2% of the population of England screened positive for the condition.

### **Valproate:**

- Valproate (sodium valproate or valproic acid) is an anti-epileptic medicine. The semi-sodium salt of valproate is also used in patients with bipolar disorder.
- Medicines containing valproate have been available since the late 1960s. They are marketed in many countries world-wide, including in all European Union (EU) Member States, under various trade names including under the Sanofi brand names, Epilim, Depakine and Depakote, and as generic medicines.
- Valproate is a highly effective drug for the treatment of generalised and partial epilepsies, and for some patients, suffering from certain forms of resistant epilepsies, including some women of child-bearing potential, it remains the only effective therapeutic option.

## **INTRODUCTION**

### **Sanofi**

Sanofi is a global life sciences company. Our aim is to make available to healthcare professionals (HCPs) and patients medicines to support tens of millions of people across the UK in the moments that matter, helping people live longer, live better and experience life to the fullest. With over 1,750 employees in the



UK, we have a strong presence to support the needs of patients.

#### Independent Medicines & Medical Devices Safety Review

Sanofi is sympathetic to the difficulties experienced by children with congenital abnormalities or learning difficulties and their families. Patient health is Sanofi's primary concern and we are, therefore, keen to engage with this review in its consideration of valproate.

We have provided information to assist the 'Call for Evidence' process. The information provided is focussed on the UK and reflects the timeline set by the Review for us to respond and the length of the period that has elapsed since valproate was first supplied in the UK.

We responded to the Draft Terms of Reference for this review in July 2018 and have made ourselves available to the review team throughout this process.

#### **Sanofi currently has two branded valproate-based medicines licensed for the UK market for the treatment of epilepsy and bipolar disorder:**

##### Epilim (sodium valproate/sodium valproate and valproic acid)

Is a branded medicine licensed, marketed and sold in the UK for the treatment of generalised, partial or other epilepsy. Epilim comes in tablet, syrup and liquid form for oral administration. There is also an injectable formulation, indicated for the treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

##### Depakote (semi-sodium valproate)

Is licensed, marketed and sold in the UK for the treatment of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after a manic episode could be considered in patients who have responded to Depakote for acute mania. Depakote comes in tablet form.

#### **OVERALL STATEMENT**

##### **Valproate is an essential medicine as defined by the WHO:**

- It remains one of the most effective treatments in generalised epilepsy and, for some patients suffering from certain resistant epilepsies, it is the only treatment to provide adequate seizure control.
- Valproate is an important treatment that thousands of men and women in the UK continue to rely on to control seizures during their lifetime. The health risks from poor control of seizures should not be underestimated.
- During the most recent Article 31 EU referral, which concluded this year, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) consulted widely and extensively in relation to use of valproate, and concluded that the benefit-risk balance of the product remains favourable, taking into account the agreed amendments to the product information and other risk minimisation measures.

##### **Sanofi has, at all material times, communicated the risk associated with valproate, as approved by regulatory authorities, consistent with the medical and scientific knowledge available at the time:**

- The scientific evidence in relation to the risks of valproate and other anti-epileptic drugs, when used

during pregnancy has taken many years to evolve, as a consequence of the substantial ethical difficulties associated with clinical research in pregnant women and the multiple confounding factors which may affect outcomes (including different epilepsy syndromes and seizures, other medical conditions and medicines and environmental factors). These difficulties are magnified in the context of any investigation of developmental delay or autism spectrum disorders where problems may not be identified until some time after the birth of the affected child and the role of events and exposures during early childhood is uncertain.

- Processes for the reporting of adverse effects associated with use of medicinal products have been in place at all times while valproate-containing products have been supplied in the UK. Sanofi has fully complied with these processes as they have developed over time.
- Sanofi has ensured - and continues to ensure - that reports of adverse effects, emerging safety concerns and scientific data are promptly reported to the regulatory authorities, consistent with pharmacovigilance obligations so that the benefit risk profile of valproate products may be kept under constant review in the context of product information and other risk minimisation measures.
- As knowledge regarding valproate has developed, Sanofi has regularly reviewed and updated the product information (especially the SmPCs and the PILs), as approved by the regulatory authorities, so that HCPS and patients receive information on usage based on contemporaneous scientific and medical evidence.

**Sanofi works under the supervision of the regulators so that the risks associated with valproate use during pregnancy are appropriately communicated to patients, doctors and pharmacists:**

- Sanofi participated in the Public Hearing held by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee, in September 2017, as part of a review of the safety of valproate-containing medicines in women and girls who are pregnant or of childbearing potential. At this hearing, Sanofi suggested a number of measures to support risk minimisation, including the introduction of a pregnancy prevention programme and the use of regular (at least annual) treatment reviews.
- In 2018, Sanofi worked with the Medicines and Healthcare Products Regulatory Agency (MHRA) to implement the measures recommended by the PRAC following its review and promptly to produce and distribute over 150,000 copies of the new risk minimisation materials, to all HCPs, including GPs, neurologists, epilepsy nurses and pharmacists, to ensure HCPs and patients are aware of the new contraindications to the use of valproate in pregnant women with epilepsy, unless specific conditions are met and requirements for a pregnancy prevention programme in women of child bearing potential.
- Sanofi has also participated in various initiatives to increase knowledge, understanding and awareness among HCPs and patients, beyond updates to SmPCs and PILs, both now and in the past. Notably, Sanofi has provided financial support to research and increased access to all relevant new information, consistent with the approved SmPC. By way of example, in 2017 Sanofi developed a tool for the NHS IT dispensing systems that uses a pop-up alert for pharmacists considering dispensing valproate for women of childbearing potential. Sanofi is pleased that the pop-up alert system Sanofi has developed has been taken up by NHS Digital to include on GP prescribing systems. Sanofi is currently producing separate HCP and patient-facing websites, and taking part in conferences and seminars to help explain the new risk minimisation requirements to HCPs.

**Historic context is needed:**

While we understand the Review wishes to assess the historic evidence relating to the regulatory approval of valproate medicinal products and the decision making and actions taken based on the medical and scientific knowledge at various times, we ask that the evidence is examined in the context of the

contemporaneous regulatory requirements, the available alternative treatments throughout the time, the approaches to communication of information to patients which were regarded as appropriate at various times and the cultural norms of that time.

It would not be fair or true to the evidence and facts of the situation of the time for the review to seek to make recommendations based on current views and standards and with the benefit of hindsight of what 'should' have happened: Terms of Reference 'Scope of the Review' and section 'B Sodium Valproate', paragraph ii.

Moreover, the Review will need to take into account the fact that epilepsy is a serious medical condition associated with important implications and risks when inadequately treated and to consider the availability of treatments other than valproate at material times, as well as the developing scientific knowledge regarding use in pregnancy.

#### **Expert involvement in the Review:**

It is currently unclear which persons and bodies have been contacted by the review. However, given the range and scope of the issues identified, we believe significant expert involvement will help inform and better equip the review in its considerations of these matters. The involvement of scientific, clinical and patient representative bodies in the European Medicines Agency's public hearing, as part of their overall review into valproate use in women of childbearing potential last year, was a good example of the full range of stakeholders and key opinion leaders contributing to a greater and balanced understanding of this complex area and therefore to well-informed decision-making.

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<sup>i</sup> Epilepsy Action. Epilepsy facts, figures and terminology. <https://www.epilepsy.org.uk/press/facts>. Accessed on 19 Oct 18

<sup>ii</sup> British National Formulary. September 2018.

<sup>iii</sup> National Sentinel Clinical Audit of Epilepsy-related deaths, 2002.

<sup>iv</sup> Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics. September 2011

<sup>v</sup> Bebbington and Ramana. The epidemiology of bipolar affective disorder. *Social Psychiatry and Psychiatric Epidemiology*. 1995; 30(6): 270-292

<sup>vi</sup> Adult Psychiatric Morbidity Survey. Mental health and wellbeing in England. 2014



Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence. Reference: AZNFVK. Oct 18

## Response to Question 1

**Please confirm the valproate-containing medications that you, or any subsidiary currently hold or have ever held marketing authorisation for within Europe.**

Please see below Marketing Authorisations held in the UK for valproate containing products. The company holds licences for a range of Epilim preparations indicated for the treatment of epilepsy, and Depakote, which is indicated for use in bipolar disease. The original product licence for Epilim was granted to Pharmacy Products UK Ltd, trading as Reckitt-Labaz and the products were acquired by Sanofi in 1981. The first table provides details of current Marketing Authorisations and the second provides information on previous marketing authorisations held that have since been cancelled. The date of first registration of these licences is also included in the table (providing the information requested in Question 2b).

MA number	Product name	Active ingredients	Dosage form	License issue date
PL 04425/0300	EPILIM LIQUID	SODIUM VALPROATE	Oral solution	07/05/1983
PL 04425/0301	EPILIM SYRUP	SODIUM VALPROATE	Syrup	09/07/1976
PL 04425/0302	EPILIM 200 GASTRO-RESISTANT TABLETS	SODIUM VALPROATE	Gastro-resistant tablet	02/27/1980
PL 04425/0303	EPILIM 500 GASTRO-RESISTANT TABLETS	SODIUM VALPROATE	Gastro-resistant tablet	10/26/1977
PL 04425/0317	EPILIM 100MG CRUSHABLE TABLETS	SODIUM VALPROATE	Tablet	05/25/1983
PL 04425/0685	EPILIM 400MG POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION	SODIUM VALPROATE	Powder and solvent for solution for injection	05/05/1988
PL 04425/0307	EPILIM CHRONO 200MG CONTROLLED RELEASE TABLETS	SODIUM VALPROATE; VALPROIC ACID	Prolonged-release tablet	08/31/1993
PL 04425/0308	EPILIM CHRONO 300 CONTROLLED RELEASE TABLETS	SODIUM VALPROATE; VALPROIC ACID	Prolonged-release tablet	11/12/1991
PL 04425/0309	EPILIM CHRONO 500MG CONTROLLED RELEASE TABLETS	SODIUM VALPROATE; VALPROIC ACID	Prolonged-release tablet	08/31/1993
PL 04425/0310	EPILIM CHRONOSPHERE MR 50MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0312	EPILIM CHRONOSPHERE MR 100MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0313	EPILIM CHRONOSPHERE MR 250MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0314	EPILIM CHRONOSPHERE MR 500MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0315	EPILIM CHRONOSPHERE MR 750MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0316	EPILIM CHRONOSPHERE MR 1000MG MODIFIED RELEASE GRANULES	SODIUM VALPROATE; VALPROIC ACID	modified release granules	07/11/2006
PL 04425/0199	DEPAKOTE 250MG TABLETS	VALPROATE SEMISODIUM	Gastro-resistant tablet	12/21/2000
PL 04425/0200	DEPAKOTE 500MG TABLETS	VALPROATE SEMISODIUM	Gastro-resistant tablet	12/21/2000



**Previous Marketing Authorisations – now cancelled**

MA number	Product name	Active ingredients	Dosage form	License issue date	Cancellation date
PL 0623/0001	LABAZENE (EPILIM TABLETS)	SODIUM VALPROATE	Tablet	02/08/1972*	Not available
PL 11723/0371	VALPROLIM (DEPAKOTE)	VALPROATE SEMISODIUM	Gastro-resistant tablet	08/20/1985	09/30/2008
PL 11723/0372	VALPROLIM (DEPAKOTE)	VALPROATE SEMISODIUM	Gastro-resistant tablet	08/20/1985	09/30/2008
PL 11723/0373	VALPROLIM (DEPAKOTE)	VALPROATE SEMISODIUM	Gastro-resistant tablet	08/20/1985	09/30/2008
PL 17780/0065	SODIUM VALPROATE	SODIUM VALPROATE	Oral solution	10/20/1994	03/23/2018
PL 17780/0453	SODIUM VALPROATE	SODIUM VALPROATE	Gastro-resistant tablet	09/30/1994	03/23/2018
PL 17780/0454	SODIUM VALPROATE	SODIUM VALPROATE	Gastro-resistant tablet	09/30/1994	03/23/2018
PL 17780/0239	MAPHILEP 200MG MR TABLETS	SODIUM VALPROATE ; VALPROIC ACID	Modified-release tablet	08/30/2007	05/18/2011
PL 17780/0239	MAPHILEP 300MG MR TABLETS	SODIUM VALPROATE ; VALPROIC ACID	modified-release tablet	08/30/2007	05/18/2011
PL 17780/0239	MAPHILEP 500MG MR TABLETS	SODIUM VALPROATE ; VALPROIC ACID	Modified-release tablet	08/30/2007	05/18/2011

\* PL 0623/001 was originally granted for a period of one year, and was due for renewal on 2 August 1973. The brand name of the product was changed from Labazene to Epilim Tablets shortly after the initial product licence was granted. A full licence was issued on 28 October 1974, for 5 years backdated to 2 August 1973.



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## Response to Question 2

Please provide detail for each marketing authorisation of valproate containing medication:

### (A) PREMARKET TESTING UNDERTAKEN

Valproic acid was first synthesised in 1881 for use as a laboratory solvent. In 1962, scientists working at a small French pharmaceutical company, the Laboratoires Berthier, discovered that the compound had substantial ability to prevent seizures and it was subsequently investigated as an anticonvulsant. Further research was carried out in France and an application for registration was submitted to the French Minister for Public Health in November 1966.

The French application for registration was approved in 1967, with the authorised therapeutic indications of: a) generalised or focalised epilepsies and b) personality or character disorders linked to epilepsy. Sodium valproate was introduced onto the French market towards the end of 1967.

Laboratoires Berthier subsequently entered into a licensing agreement with the Belgian company, Labaz for the supply of sodium valproate in Belgium, Holland, Luxembourg, West Germany and Spain. By the end of December 1969, Labaz had acquired 80% of the shares in Laboratoires Berthier.

Further clinical trials were carried out by Labaz in the UK and these confirmed the results of earlier European studies, that sodium valproate was effective in reducing the incidence of seizures in patients with petit mal, grand mal, myoclonic and akinetic epilepsy and photosensitive epilepsy, including in patients with long standing epilepsy that had proved refractory to other therapies.

A review of both the European and UK literature (Simon and Penry. "Sodium di-N-propylacetate (DPA) in the treatment of epilepsy". *Epilepsia* 1975; 16: 549) found that, of a total of 1116 patients suffering from generalised, partial, mixed, myoclonic, infantile and absence seizures, 509 (45.7%) had a reduction in seizure frequency of 75-100% and 284 (25.4%) had a reduction of 33-74%. 323 patients (28.9%) had a less than 33% reduction in seizure rate. Further studies confirmed the usefulness and effectiveness of sodium valproate as sole therapy for many types of epilepsy.

Certain adverse effects were found to be associated with administration, particularly gastro intestinal symptoms (indigestion, heartburn and nausea). The development of an enteric coated formulation reduced the incidence of these effects.

An application for a full product licence in the UK was submitted to the DHSS Medicines Division by Reckitt & Colman (R&C) on behalf of Pharmacy Products UK Ltd, trading as Reckitt-Labaz Ltd, in September 1973. The results of a teratology study in rats and mice, which demonstrated some



teratological effects at high doses, toxic to the mother, but not at doses recommended for humans, were described in the application. However R&C advised the DHSS that, while sodium valproate had been marketed in five European countries for up to 4 years, no reports of congenital abnormalities in infants exposed to the product during pregnancy had been received.

The first product licence in the UK was limited to a period of one year; a condition of the licence required all patients to be monitored for efficacy and safety and the results to be reported to the Licensing Authority in writing at 6 months and again at 10 months after grant of the licence. During this period R&C provided the results of other teratology studies that had been carried out in rats, mice and rabbits. A full licence was issued on 28 October 1974, for 5 years from 2 August 1973.

The licence was subject to conditions imposed by the Licensing Authority following its consideration of the data from animal studies in relation to sodium valproate. The licence set out the mandatory words which were required to be used by the company in the data sheet and in any materials promoting the product to doctors:

*“(a) Under “Uses” the licence shall read “for use in generalised focal or other epilepsy. In women of child bearing age, the product should only be used in severe cases or those resistant to other treatment”.*

*(b) The following warning shall be included in the data sheet and in all promotional material for this product (i.e. mailings, journal advertisements, literature handed out by representatives etc.):-*

*“Women of childbearing age: This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.”*

**(B) DATE OF LICENSING**

Please see the table presented in response to Question 1 which gives the date of licensing in the UK for the different formulations of valproate containing products registered by Sanofi or Sanofi heritage companies.

**(C) ANY DOSE OR FORMULATION CHANGES**

A number of new presentations of Epilim have been introduced in the UK over the lifetime of the product. Dates of first registration of these products are provided in response to Question 1. There have also been various small changes to the method of manufacture for the different products over their lifetime.

At all times, valproate medicines supplied in the UK have been available only on the basis of a prescription issued by an appropriately qualified healthcare professional (HCP), who determines



the suitability of the treatment, the dosing regimen and, where relevant, the choice of formulation.

General dosage recommendations have remained broadly consistent over the lifetime of the product, and are tailored by the prescribing HCP to individual patient circumstances.

Epilim

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

The first datasheet for Epilim 200mg tablets indicated that dosing should start with 1 tablet three times daily, increasing over time until optimum control was obtained. There were no specific dosing instructions for use during pregnancy.

The information provided has been updated over time to indicate that the lowest effective dose should be used during pregnancy, and it should be given as divided doses. An outline of those updates is provided in the table below. They should be considered together with the warnings provided in the datasheets/ SmPCs and set out at section F below.

Date added	Wording concerning dosage in pregnancy
1993/94 Datasheet Compendium	<p><b>Pregnancy</b> In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.”</p>
1994/95 Datasheet Compendium	<p><b>Pregnancy</b> The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.</p>
1998/99 Datasheet Compendium	<p><b>Pregnancy</b> The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.</p>

Date added	Wording concerning dosage in pregnancy
2003 SmPC	<p><b>4.6 Fertility, pregnancy and lactation</b></p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</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 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.</p>
2011 SmPC	<p><b>4.6 Fertility, pregnancy and lactation</b></p> <p>Rewording:</p> <ul style="list-style-type: none"> <li>• In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.</li> </ul> <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 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.</p>
2012 SmPC	<p><b>4.6 Fertility, pregnancy and lactation</b></p> <p>Added:</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.</p>
2015 SmPC	<p>information moved to posology section:</p> <p><b>4.2 Posology and method of administration</b></p> <p>Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the</p>

Date added	Wording concerning dosage in pregnancy
	<p>lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses</p> <p><b>4.6 Fertility, pregnancy and lactation</b>  Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:</p> <ul style="list-style-type: none"> <li>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentration</li> </ul>
2018 SmPC	<p><b>4.2 Posology and method of administration</b></p> <p><u>Female children and women of childbearing potential</u></p> <p>Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).</p> <p>Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).</p> <p>Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).</p> <p><b>4.6 Fertility, pregnancy and lactation</b>  If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:</p> <ul style="list-style-type: none"> <li>• Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.</li> <li>• The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations (see section 4.2).</li> </ul>

## Depakote

The current dosing instructions for Depakote prescribed for the treatment of Bipolar Disorder, state that the daily dosage should be established according to age and body weight. There is wide variation in individual sensitivity which also should be considered. The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight had shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 – 2000 mg of valproate. Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.

The information provided has been updated over time to indicate that the lowest effective dose should be used during pregnancy, and it should be given as divided doses. An outline of those updates is provided in the table below.

Date added to SmPC	Wording concerning dosage in pregnancy
2000	The available evidence suggests that 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.
2003	<p><b>4.6 Fertility, pregnancy and lactation</b></p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>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.</p>
2012	<p><b>4.6 Fertility, pregnancy and lactation</b></p> <p>Added:</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.</p>
2015	<p>information moved to posology section:</p> <p><b>4.2 Posology and method of administration</b></p> <p>Depakote should be initiated and supervised by a specialist experienced in the management of bipolar disorder. Treatment should only be initiated if other</p>

Date added to SmPC	Wording concerning dosage in pregnancy
	<p>treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Depakote should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses</p> <p><b>4.6 Fertility, pregnancy and lactation</b>  Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of bipolar disorder. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:</p> <ul style="list-style-type: none"> <li>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentration</li> </ul>
2018	<p><b>4.2 Posology and method of administration</b></p> <p><u>Female children and women of childbearing potential</u></p> <p>Valproate must be initiated and supervised by a specialist experienced in the management of bipolar disorder. Valproate should not be used in female children or women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).</p> <p>Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefit and risk should be carefully reconsidered at regular treatment reviews (see section 4.4).</p> <p>Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).</p>

**(D) ANY CHANGES TO INDICATION**

The indication for Epilim remains consistent with the initial product licence, namely, for the treatment of generalized, partial or other epilepsy.

Depakote was authorised in December 2000 for the acute treatment of a manic episode associated with bipolar disorder. In November 2010 the indication was modified to the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania.

**(E) CONTRAINDICATIONS THAT HAVE BEEN ADDED**

Epilim

When Valproate was first registered, there were no specific contraindications; the September 1974 Data Sheet contained the following information in relation to pregnancy:

***“Uses***

*...In women of child bearing age, the product should only be used in severe cases or in those resistant to other treatment.”*

***“CONTRA-INDICATIONS, WARNINGS, ETC***

***Precautions - women of childbearing age***

*This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.”*

The current contraindications for Epilim (together with the dates they were added to the Summary of Product Characteristics (SmPC)) are shown below.

<b><i>Date added:</i></b>	<b><i>Contraindication:</i></b>
1991	Hypersensitivity to sodium valproate. Active liver disease. Personal or family history of severe hepatic dysfunction, especially drug related.
1996	Porphyria
2015	Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase $\gamma$ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder
2016	Patients with known urea cycle disorders
2018	In pregnancy unless there is no suitable alternative treatment* In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled

Depakote

When Depakote was authorized in 2000, the contraindications included in the SmPC reflected those listed for Epilim at that time. All additional contraindications to use of Epilim introduced since that time have also been applied to Depakote.

In addition, to the above, following the recent PRAC review, the Depakote has also been contraindicated in the following circumstances:

- In pregnancy
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled



**(F) WARNINGS THAT HAVE BEEN ADDED**

**EPILIM**

There have been a number of warnings added to the Epilim Data Sheet /SmPC over the years. The information provided in this section focusses on those warnings related to women of childbearing potential and pregnancy.

For 1974 through to 2000, information is provided as presented in the published Datasheet Compendia, which were published on an annual basis. They therefore present a “snapshot” in time. When information was updated between the annual printed versions of the Compendia, then this was available to HCPs on request from the Company.

From 2000, the Datasheet Compendia became available on-line and could be updated with new information as changes were approved for the licence. Data are therefore presented from this time onwards from when the variation was approved and could be made immediately available electronically.

The information below is provided for Epilim 200mg enteric coated tablet, which is representative of the information provided across the range of valproate products. (Note: for 1974-1981, Epilim plain 200mg tablets were available and were subsequently replaced by 200mg enteric coated tablets.)

<b><i>Date in Compendium</i></b>	<b><i>Information in data sheet</i></b>
1974 -76	<p>“Uses</p> <p>In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment.”</p> <p>“Contra-indications, warnings, etc.</p> <p>“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.”</p>
1977- 81	<p>“Uses</p> <p>In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.”</p> <p>“Contra-indications, warnings, etc.</p> <p>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</p>

<i>Date in Compendium</i>	<i>Information in data sheet</i>
	suggested by these findings.”
1982-83	<p>“Uses</p> <p>In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment.”</p> <p>Women of child-bearing age: Valproic acid or sodium valproate, like certain other anticonvulsants, have 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.”</p>
1984-90	<p>In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment.”</p> <p>“Contra-indications, warnings, etc.</p> <p>Women of child-bearing age: Valproic acid or 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 and their pregnancies should be carefully monitored”.</p>
1989-90	<p><b>Note:</b> A licence for Epilim intravenous formulation was approved during 1988, and different wording was approved in the pregnancy section compared with the other licenced formulations, The Datasheet compendium entry for Epilim Intravenous in 1989/90 was as follows:</p> <p>Some studies have demonstrated an increase in the expected incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated.</p> <p>There is evidence of teratogenic effects with anticonvulsants including Epilim in animals and there have been reports of congenital abnormalities in offspring of a small number of epileptic patients receiving therapy during pregnancy.</p> <p>In pregnancy, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored.”</p>
1990-92	<p>(wording now in line for all Epilim formulations)</p> <p>“<b>Women of child-bearing age.</b></p> <p>An increased incidence of congenital abnormalities in off-spring born to mothers</p>

<b>Date in Compendium</b>	<b>Information in data sheet</b>
	<p>with epilepsy both untreated and treated has been demonstrated.</p> <p>There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.</p> <p>In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and the patients should be informed of these and the need for screening”.</p>
1993-94	<p><b>“Use in Pregnancy and Lactation</b></p> <p>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.</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%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.</p> <p>In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.”</p>
1994-97	<p><b>“Use in Pregnancy and Lactation</b></p> <p>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.</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%.</p> <p>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, 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</p>

<b>Date in Compendium</b>	<b>Information in data sheet</b>
	<p>continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate”.</p>
1998-99	<p>Uses in Pregnancy and Lactation: (- changes highlighted in text)</p> <p>An increased incidence of congenital abnormalities (including facial dysmorphism, neural tube defects and multiple malformations, <b>particularly of the limbs</b>) 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 <b>1 to 2%</b>.</p> <p>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, <b>in divided doses</b> as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate”.</p>
1999-2000	<p>Amendments to include a warning for haemorrhagic syndrome were added</p> <p>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken 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 inducing drugs. Platelet count, fibrinogen plasma level, coagulation tests and coagulation status should be investigated in neonates.”</p>

<b>Date</b>	<b>SmPCs introduced</b>
2001	<p><b>Changes in order to comply with the EU Commission guideline on SmPCs</b></p> <p>Removal of restriction in Indications section of data sheet</p>

Date	SmPCs introduced
	<ul style="list-style-type: none"> <li>• Inclusion of following text in section 4.4:  <p>“It is recommended that Epilim be used in women of child bearing age only in severe cases or those resistant to other treatment because of the potential teratogenic risk to the foetus exposed to valproate in utero. Women of child bearing age should be informed of the potential risks and benefits of continuing antiepileptic treatment throughout pregnancy (see also section 4.6 “Pregnancy and Lactation”)</p> </li> <li>• Section 4.6 was unchanged as approved on 19 September 1997  <p>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 to 2%.</p> <p>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 alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate”.</p> <p>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken 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 inducing drugs. Platelet count, fibrinogen plasma level, coagulation tests and coagulation status should be investigated in neonates.”</p> </li> </ul>
2003	<p><b>“4 Clinical Particulars”</b></p> <p><b>"4.4 Special Warnings and Special Precautions for Use:</b></p> <p>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 ±</p>

Date	SmPCs introduced
	<p>myoclonus/photosensitivity. For partial epilepsy, Epilim should only be used 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).”</p> <p><b>"4.6 Pregnancy and Lactation:</b></p> <p>4.6.1 Pregnancy</p> <p>From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:</p> <ul style="list-style-type: none"> <li>- Risk associated with epilepsy and antiepileptics</li> </ul> <p>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.</p> <p>Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.</p> <ul style="list-style-type: none"> <li>- Risk associated with valproate</li> </ul> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.</p> <p>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%.</p>

Date	SmPCs introduced
	<p>In view of the above data:</p> <p>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.</p> <p>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.</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 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.</p> <p>During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.</p> <p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).</p> <p>- Risk in the neonate</p> <p>Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.</p> <p>Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates</p>
2005	<p><b>“4. Clinical Particulars</b></p> <p><b>4.4 Special warnings and precautions for use</b></p>

Date	SmPCs introduced
	<p>4.4.2 Precautions</p> <p>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> <p><b>4.6 Use during pregnancy and lactation</b></p> <p>Women of childbearing potential should not be started on Epilim without specialist neurological advice.</p> <p>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.</p> <p>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.</p> <p>If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.</p> <p>When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")</p> <p><b>4.6.1 Pregnancy</b></p> <p>From experience in treating mothers with epilepsy, the risk associated with the use of Epilim during pregnancy has been described as follows:</p> <p>- <b>Risk associated with epilepsy and antiepileptics</b></p> <p>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 cardiovascular malformations.</p> <p>Epidemiological studies have suggested an association between in-utero exposure to Epilim and a risk of developmental delay. Developmental delay has been reported in</p>

Date	SmPCs introduced
	<p>children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.</p> <p><b>- Risk associated with valproate</b></p> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate.</p> <p>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.</p> <p><b>- In view of the above data</b></p> <p>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.</p> <p>Folate supplementation, <b>prior</b> 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.</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 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</p>

Date	SmPCs introduced
	<p>release formulation is preferable in order to avoid high peak plasma levels.</p> <p>During pregnancy, Epilim anti-epileptic treatment should not be discontinued if it has been effective.</p> <p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).</p> <p><b>- Risk in the neonate</b></p> <p>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.</p> <p>Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.”</p> <p><b>Note section 4.8 lists</b> “Congenital and familial/genetic disorders” under “Undesirable effects” with a reference to section 4.6).</p>
2010	<p>Section 4.4</p> <p><b><u>Special warnings:</u> 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).</b></p> <p><b><u>Precautions:</u> Pregnancy:</b> Women of childbearing potential should not be started on Epilim without specialist neurological advice. <b>Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential</b> regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).</p> <p>Section 4.6 Women of childbearing potential should not be started on Epilim without specialist neurological advice.</p>

Date	SmPCs introduced
	<p>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.</p> <p>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.</p> <p>If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.</p> <p>When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled “In view of the above”)</p> <p><b>4.6.1 Pregnancy</b>  <b>- Risk associated with epilepsy and antiepileptics</b>  In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.</p> <p>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.</p> <p>Antiepileptic drugs should be withdrawn under specialist supervision.</p> <p>- <i>Risk associated with seizures</i>  During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.</p> <p>- <b><i>Risk associated with valproate</i></b>  In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.  In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies</p>

Date	SmPCs introduced
	<p>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.</p> <p>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.</p> <p>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>Autism spectrum disorders have also been reported in children exposed to valproate in utero.</p> <p><b>- In view of the above data</b></p> <p>When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy.</p> <p>Folate supplementation, <b>prior</b> 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.</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 and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily.</p> <p>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.</p> <p>During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk.</p>

Date	SmPCs introduced
	<p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).</p> <p><b>- Risk in the neonate</b></p> <p>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.</p> <p>Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.</p>
2011	<p>Section 4.4 updated:  <u>Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.</u></p> <p>Section 4.6  <u>SPC updated only in few categories as shown below:</u></p> <p><u>Risk associated with valproate</u></p> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.</p> <p>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</p>

Date	SmPCs introduced
	<p>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>Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.</p> <p>Autism spectrum disorders have also been reported in children exposed to valproate in utero.</p> <p><u>In view of the above data</u></p> <p><b>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 childbearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy.</b></p> <p><b>If a women plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication:</b></p> <ul style="list-style-type: none"> <li>• <b>In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.</b></li> <li>• <b>In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.</b></li> <li>• <b>Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.</b></li> </ul> <p><b>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.</b></p> <p><b>Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).</b></p>

Date	SmPCs introduced
	<p><u>Risk in the neonate</u>            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.</p> <p><b>Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.</b></p>
2012	<p>Section 4.6  <b><u>SPC updated only in few categories as shown below:</u></b></p> <p><u>Risk associated with valproate</u>            In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.            There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.            In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. <b>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.</b></p> <p>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>Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.</p>

Date	SmPCs introduced
	<p>Autism spectrum disorders have also been reported in children exposed to valproate in utero. .....</p> <p><b><u>Risk in the neonate</u></b> Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors; afibrinogenemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates. Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy. <b>Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.</b></p>
2015	<p>As a result of the PRAC review the information in the SmPC was updated and all relevant warning text related to pregnancy is re-produce below.</p> <p><b>Section 4.2 Posology and method of administration</b></p> <p><u>Female children, female adolescents, women of childbearing potential and pregnant women</u></p> <p>Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.</p> <p><b>Section 4.4.1. Special Warnings</b></p> <div style="border: 1px solid black; padding: 5px;"> <p><b>Female children/Female adolescents/Women of childbearing potential/ Pregnancy:</b></p> <p>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.</p> </div>

Date	SmPCs introduced
	<p>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.</p> <p>In particular the prescriber must ensure the patient understands:</p> <ul style="list-style-type: none"> <li>• The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.</li> <li>• The need to use effective contraception.</li> <li>• The need for regular review of treatment.</li> <li>• The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.</li> </ul> <p>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).</p> <p>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.</p> <p><b>Section 4.4.2 Precautions</b></p> <p>Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).</p> <p><b>Section 4.6. Fertility, pregnancy and lactation</b></p> <p>Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.</p> <p><i>Pregnancy Exposure Risk related to valproate</i></p> <p>Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital</p>

Date	SmPCs introduced
	<p>malformations than valproate monotherapy.</p> <p><i>Congenital malformations</i>            Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 - 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.</p> <p>Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.</p> <p><i>Developmental disorders</i>            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.</p> <p>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.</p> <p>Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes.</p> <p>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.</p> <p>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><i>Female children, female adolescents and woman of childbearing potential (see above and section 4.4)</i></p>

Date	SmPCs introduced
	<p data-bbox="394 323 857 359"><i>If a Woman wants to plan a Pregnancy</i></p> <ul data-bbox="394 396 1406 604" style="list-style-type: none"> <li>• During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.</li> <li>• In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed</li> <li>• In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.</li> </ul> <p data-bbox="394 646 1406 747">Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.</p> <p data-bbox="394 789 1406 856">If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:</p> <ul data-bbox="443 898 1406 1247" style="list-style-type: none"> <li>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.</li> <li>- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</li> <li>- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.</li> </ul> <p data-bbox="394 1289 623 1318"><i>Risk in the neonate</i></p> <ul data-bbox="443 1325 1406 1883" style="list-style-type: none"> <li>- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.</li> <li>- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.</li> <li>- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.</li> <li>- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken</li> </ul>

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	<p>valproate during the last trimester of their pregnancy.</p> <p><i>Breastfeeding</i> Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).</p> <p>A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.</p> <p><i>Fertility</i> Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.</p> <p><b>Section 4.8. Undesirable Effects</b> Congenital malformations and developmental disorders (see section 4.4 and section 4.6).</p>
2018	<p>As a result of the PRAC review the information in the SmPC was updated and all relevant warning text related to pregnancy is re-produced below.</p> <p><b>4.2 Posology and method of administration</b></p> <p><u>Female children and women of childbearing potential</u></p> <p>Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).</p> <p>Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).</p> <p>Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).</p> <p><b>4.3 Contraindications</b></p> <p>Epilim is contraindicated in the following situations:</p> <ul style="list-style-type: none"> <li>• In pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).</li> <li>• In women of childbearing potential unless the conditions of the pregnancy</li> </ul>

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	<p style="text-align: center;">prevention programme are fulfilled (see sections 4.4 and 4.6).</p> <p><b>4.4 Special warnings and precautions for use</b></p> <p><b>4.4.1 Special warnings</b></p> <p style="text-align: center;"><i>Female children, women of childbearing potential and pregnant women:</i></p> <div style="border: 1px solid black; padding: 5px;"> <p><b><u>Pregnancy Prevention Programme</u></b></p> <p>Valproate has a high teratogenic potential and children exposed <i>in utero</i> to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).</p> <p>Epilem is contraindicated in the following situations:</p> <ul style="list-style-type: none"> <li>• In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).</li> <li>• In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).</li> </ul> <p><b><u>Conditions of Pregnancy Prevention Programme:</u></b></p> <p>The prescriber must ensure that:</p> <ul style="list-style-type: none"> <li>• Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.</li> <li>• The potential for pregnancy is assessed for all female patients.</li> <li>• The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate <i>in utero</i>.</li> <li>• The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.</li> <li>• The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.</li> <li>• The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.</li> <li>• The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.</li> <li>• The patient understands the need to urgently consult her physician in case</li> </ul> </div>

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	<p>of pregnancy.</p> <ul style="list-style-type: none"> <li>• The patient has received the Patient Guide.</li> <li>• The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).</li> </ul> <p>These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.</p> <p><u>Female children</u></p> <p>The prescriber must ensure that:</p> <ul style="list-style-type: none"> <li>• The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.</li> <li>• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate <i>in utero</i>.</li> </ul> <p>In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.</p> <p><u>Pregnancy test</u></p> <p>Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.</p> <p><u>Contraception</u></p> <p>Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual</p>

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	<p>circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on effective contraception.</p> <p><u>Annual treatment reviews by a specialist</u></p> <p>The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.</p> <p><u>Pregnancy planning</u></p> <p>If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.</p> <p><u>In case of pregnancy</u></p> <p>If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).</p> <p><u>Pharmacists must ensure that:</u></p> <ul style="list-style-type: none"> <li>• The Patient Card is provided with every valproate dispensation and that patients understand its content.</li> <li>• Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.</li> </ul> <p><u>Educational materials</u></p> <p>In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the</p>

Date	SmPCs introduced
	<p>Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.</p> <p>An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.</p> <p>Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy.</p> <p><b>4.6 Fertility, pregnancy and lactation</b></p> <ul style="list-style-type: none"> <li>• Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.</li> <li>• Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).</li> </ul> <p><i>Pregnancy exposure risk related to valproate</i> Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.</p> <p><u>Teratogenicity and developmental effects</u></p> <p><i>Congenital malformations</i> Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.</p> <p>Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.</p> <p><i>Developmental disorders</i></p>

Date	SmPCs introduced
	<p>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.</p> <p>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.</p> <p>Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.</p> <p>There are limited data on the long term outcomes.</p> <p>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.</p> <p>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><i>Female children and woman of childbearing potential (see above and section 4.4)</i></p> <p><i>If a woman plans a pregnancy</i>  If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.</p> <p><i>Pregnant women</i>  Valproate as treatment for epilepsy is contraindicated in pregnancy unless</p>

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	<p>there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.</p> <p>During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:</p> <ul style="list-style-type: none"> <li>• Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.</li> <li>• The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations (see section 4.2).</li> </ul> <p>All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</p> <p><u>Risk in the neonate</u></p> <ul style="list-style-type: none"> <li>• Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.</li> <li>• Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.</li> <li>• Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.</li> <li>• Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.</li> </ul>

Date	SmPCs introduced
	<p><u>Breast-feeding</u> Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).</p> <p>A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.</p> <p><u>Fertility</u> Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.</p> <p>Section 4.8 Undesirable Effects Congenital malformations and developmental disorders (see section 4.4 and section 4.6).</p>
2018	<p><b><u>Added Oestrogen warning to already existing text</u></b></p> <p>Section 4.4 <u>Oestrogen-containing products</u> Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products. On the opposite, valproate does not reduce efficacy of hormonal contraceptives.</p> <p>Section 4.5 <b><i>Oestrogen-containing products, including oestrogen-containing hormonal contraceptives</i></b> Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels. On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestrogen-containing agents in women receiving hormonal contraception.</p>

Date	SmPCs introduced
	<p>Section 4.6  <u>Oestrogen-containing products</u>            Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).</p>

### **DEPAKOTE**

When Depakote was authorised in December 2000, the pregnancy warnings were in line with those approved for Epilim at that time.

Changes in the pregnancy warnings since 2000 are set out in the table below.

Date	SmPCs introduced
2000	<p><b>Section 4.6. (Pregnancy and lactation)</b></p> <p>When used for the treatment of manic episodes the benefits of therapy should be carefully weighed against risk in treating or counselling women of childbearing potential. If Depakote is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazards to the foetus.</p> <p>When Depakote therapy is continued during pregnancy, precautions should be taken as described below.</p> <p>Experience of the use of valproate-containing products during pregnancy has been gained during the treatment of epileptic mothers.</p> <p>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 monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing</p>

Date	SmPCs introduced
	<p>Depakote treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate.</p> <p><b>Section 4.8</b> listed Teratogenic risk (see 4.6 Pregnancy)</p>
2003	<p><b>"4 Clinical Particulars"</b></p> <p><b>"4.4 Special Warnings and Special Precautions for Use:</b></p> <p>Pregnancy: Women of childbearing potential should receive specialist psychiatric advice prior to starting Depakote and if planning a pregnancy while taking Depakote because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).</p> <p><b>"4.6 Pregnancy and Lactation:</b></p> <p>4.6.1 Pregnancy</p> <p>From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:</p> <ul style="list-style-type: none"> <li>- Risk associated with valproate</li> </ul> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.</p> <p>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%.</p> <p>In view of the above data:</p> <p>Women of childbearing age should be informed of the risks and benefits of continuing Depakote treatment throughout pregnancy.</p> <p>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</p>

Date	SmPCs introduced
	<p>as contraception is discontinued.</p> <p>. 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.</p> <p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).</p> <p>- Risk in the neonate</p> <p>Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.</p> <p>Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates</p>
2004	<p>4.6.1. – information in bold added</p> <p><b>- Risk associated with valproate</b></p> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>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 treated with valproate.</p> <p>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%.</p> <p><b>Epidemiological studies, of women with epilepsy, have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment.</b></p>

Date	SmPCs introduced
2005	<p data-bbox="396 296 667 321"><b>“4. Clinical Particulars</b></p> <p data-bbox="396 359 935 384"><b>4.4 Special warnings and precautions for use</b></p> <p data-bbox="396 428 602 453">4.4.2 Precautions</p> <p data-bbox="396 497 1406 663">Pregnancy: Women of childbearing potential should not be started on Depakote without specialist psychiatric advice. Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).</p> <p data-bbox="396 707 867 732"><b>4.6 Use during pregnancy and lactation</b></p> <p data-bbox="396 774 1406 835">Women of childbearing potential should not be started on Depakote without specialist psychiatric advice.</p> <p data-bbox="396 877 1406 972">Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1).</p> <p data-bbox="396 1014 1406 1108">Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.</p> <p data-bbox="396 1150 1406 1211">If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.</p> <p data-bbox="396 1253 1406 1348">When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")</p> <p data-bbox="396 1390 1406 1589">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 cardiovascular malformations.</p> <p data-bbox="396 1631 1406 1831">Epidemiological studies have suggested an association between in-utero exposure to Depakote and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the bipolar therapy should be undertaken as this may lead to an</p>

Date	SmPCs introduced
	<p>immediate relapse of the underlying symptoms.</p> <p>4.6.1. Pregnancy</p> <p>From experience in treating mothers with epilepsy, the risk associated with the use of Depakote during pregnancy has been described as follows:</p> <p><b>- Risk associated with valproate</b></p> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate.</p> <p>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.</p> <p><b>- In view of the above data</b></p> <p>When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of childbearing age should be informed of the risks and benefits of continuing treatment throughout pregnancy.</p> <p>Folate supplementation, <b>prior</b> to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.</p> <p>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.</p>

Date	SmPCs introduced
	<p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).</p> <p><b>- Risk in the neonate</b></p> <p>Very rare cases of haemorrhagic, syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other enzyme inducing drugs.</p> <p>Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.”</p> <p><b>Note section 4.8 lists</b> “Congenital and familial/genetic disorders” under “Undesirable effects” with a reference to section 4.6).</p>
2010	<p>Section 4.4</p> <p>Special Warnings: Women of childbearing potential: This medicine should not be used in women of childbearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of childbearing potential have to use effective contraception during treatment (see also 4.6. Pregnancy and Lactation).</p> <p>Precautions: See section 4.6 Pregnancy and Lactation.</p> <p>4.6. Pregnancy and lactation This medicine should not be used during pregnancy and in women of childbearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of childbearing potential have to use effective contraception during treatment.</p> <p>4.6.1. Pregnancy</p> <p><u>Risk associated with bipolar therapy</u> This drug should be withdrawn under specialist supervision.</p> <p><b>- Risk associated with valproate</b> In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p>

Date	SmPCs introduced
	<p>In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.</p> <p>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.</p> <p>Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.</p> <p>Autism spectrum disorders have also been reported in children exposed to valproate in utero.</p> <p><b>- In view of the above data</b></p> <p>When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Depakote is prescribed for the first time or a woman already treated with Depakote is planning a pregnancy.</p> <p>Folate supplementation, <b>prior</b> to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.</p> <p>Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day is preferable in order to avoid high peak plasma levels.</p>

Date	SmPCs introduced
	<p>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for Use).</p>
2011	<p><b>Section 4.4.</b>  Special Warnings: Women of childbearing potential (see section 4.6.): This medicine should not be used in women of childbearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a woman of childbearing potential treated with Depakote plans a pregnancy. Women of childbearing potential must use effective contraception during treatment.</p> <p>Precautions: See section 4.6 Pregnancy and Lactation.</p> <p><b>Section 4.6</b>  <b>Following section revised:</b>  <i>- In view of the above data</i>  The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Depakote is prescribed for the first time, or when a women of child bearing potential treated with Depakote plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy.</p> <p>If a women plans a pregnancy or becomes pregnant, Depakote therapy should be reassessed whatever the indication:</p> <ul style="list-style-type: none"> <li>• In bipolar disorders indication, cessation of Depakote treatment should be considered.</li> <li>• In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.</li> <li>• Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.</li> </ul> <p><i>- Risk in the neonate</i>  Following statement added:  Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.</p>

Date	SmPCs introduced
2012	<p>Section 4.6  <u><b>SPC updated only in few categories as shown below:</b></u></p> <p><u>Risk associated with valproate</u>            In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.            There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.            In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. <b>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.</b>            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>Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.</p> <p>Autism spectrum disorders have also been reported in children exposed to valproate in utero.</p>
2015	<p>As a result of the PRAC review the information in the SmPC was updated and all relevant warning text related to pregnancy is re-produced below. Any substantial differences are outlined below.</p> <p><b>Section 4.2 Posology and method of administration</b></p> <p><u>Female children, female adolescents, women of childbearing potential and pregnant women</u>            Depakote should be initiated and supervised by a specialist experienced in the management of bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit</p>

Date	SmPCs introduced
	<p>and risk should be carefully reconsidered at regular treatment reviews. Preferably Depakote should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.</p> <p><b>Section 4.4.1. Special Warnings</b></p> <div style="border: 1px solid black; padding: 10px;"> <p><b>Female children/Female adolescents/Women of childbearing potential/Pregnancy:</b></p> <p>Depakote should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with 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 Depakote during pregnancy (see section 4.6). The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.</p> <p>In particular the prescriber must ensure the patient understands:</p> <ul style="list-style-type: none"> <li>• The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.</li> <li>• The need to use effective contraception.</li> <li>• The need for regular review of treatment.</li> <li>• The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.</li> </ul> <p>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).</p> <p>Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of bipolar disorder.</p> </div>

Date	SmPCs introduced
	<p><b>Section 4.4.2 Precautions</b></p> <p>Pregnancy: See section 4.6 Pregnancy and Lactation</p> <p><b>Section 4.6. Fertility, pregnancy and lactation</b></p> <p>Depakote should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.</p> <p><i>Pregnancy Exposure Risk related to valproate</i></p> <p>Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.</p> <p><i>Congenital malformations</i></p> <p>Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 - 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.</p> <p>Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.</p> <p><i>Developmental disorders</i></p> <p>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.</p> <p>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.</p>

Date	SmPCs introduced
	<p>Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes.</p> <p>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.</p> <p>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><i>Female children, female adolescents and woman of childbearing potential (see above and section 4.4)</i></p> <p><i>If a Woman wants to plan a Pregnancy</i></p> <ul style="list-style-type: none"> <li>• In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed</li> <li>• In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.</li> </ul> <p>Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of bipolar disorder. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:</p> <ul style="list-style-type: none"> <li>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.</li> <li>- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</li> <li>- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.</li> </ul> <p><i>Risk in the neonate</i></p> <ul style="list-style-type: none"> <li>- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a</li> </ul>

Date	SmPCs introduced
	<p>decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.</p> <ul style="list-style-type: none"> <li>- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.</li> <li>- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.</li> <li>- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.</li> </ul> <p><i>Breastfeeding</i> Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).</p> <p>A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Depakote therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.</p> <p><i>Fertility</i> Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.</p> <p><b>Section 4.8. Undesirable Effects</b> Congenital malformations and developmental disorders (see section 4.4 and section 4.6).</p>
2018	<p>As a result of the PRAC review the information in the SmPCs was updated and all relevant warning text related to pregnancy is re-produced below.</p> <p><b>4.2 Posology and method of administration</b></p> <p><u>Female children and women of childbearing potential</u></p> <p>Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).</p>

Date	SmPCs introduced
	<p>Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).</p> <p>Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).</p> <p><b>4.3 Contraindications</b></p> <p><b>Depakote</b> is contraindicated in the following situations:</p> <ul style="list-style-type: none"> <li>• In pregnancy (see sections 4.4 and 4.6)</li> <li>• In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).</li> </ul> <p><b>4.4 Special warnings and precautions for use</b></p> <p><b>4.4.1 Special warnings</b></p> <p><i>Female children, women of childbearing potential and pregnant women:</i></p> <div style="border: 1px solid black; padding: 5px;"> <p><b><u>Pregnancy Prevention Programme</u></b></p> <p>Valproate has a high teratogenic potential and children exposed <i>in utero</i> to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).</p> <p><b>Depakote</b> is contraindicated in the following situations:</p> <ul style="list-style-type: none"> <li>• In pregnancy (see sections 4.4 and 4.6)</li> <li>• In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).</li> </ul> <p><b><u>Conditions of Pregnancy Prevention Programme:</u></b></p> <p>The prescriber must ensure that:</p> <ul style="list-style-type: none"> <li>• Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.</li> <li>• The potential for pregnancy is assessed for all female patients.</li> <li>• The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate <i>in utero</i>.</li> <li>• The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.</li> </ul> </div>

Date	SmPCs introduced
	<ul style="list-style-type: none"> <li>• The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.</li> <li>• The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorder.</li> <li>• The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.</li> <li>• The patient understands the need to urgently consult her physician in case of pregnancy.</li> <li>• The patient has received the Patient Guide.</li> <li>• The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).</li> </ul> <p>These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.</p> <p><u>Female children</u></p> <p>The prescriber must ensure that:</p> <ul style="list-style-type: none"> <li>• The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.</li> <li>• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate <i>in utero</i>.</li> </ul> <p>In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.</p> <p><u>Pregnancy test</u></p> <p>Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing</p>

Date	SmPCs introduced
	<p>potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.</p> <p><u>Contraception</u></p> <p>Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on effective contraception.</p> <p><u>Annual treatment reviews by a specialist</u></p> <p>The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.</p> <p><u>Pregnancy planning</u></p> <p>If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.</p> <p><u>In case of pregnancy</u></p> <p>If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).</p> <p><u>Pharmacists must ensure that:</u></p> <ul style="list-style-type: none"> <li>• The Patient Card is provided with every valproate dispensation and that patients understand its content.</li> <li>• Patients are advised not to stop valproate medication and to immediately</li> </ul>

Date	SmPCs introduced
	<p>contact a specialist in case of planned or suspected pregnancy.</p> <p><u>Educational materials</u></p> <p>In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.</p> <p>An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.</p> <p>Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder.</p> <p><b>4.6 Fertility, pregnancy and lactation</b></p> <div style="border: 1px solid black; padding: 5px;"> <ul style="list-style-type: none"> <li>• Valproate is contraindicated as treatment for bipolar disorder during pregnancy</li> <li>• Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).</li> </ul> </div> <p><i>Pregnancy exposure risk related to valproate</i></p> <p>Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.</p> <p><u>Teratogenicity and developmental effects</u></p> <p><i>Congenital malformations</i></p> <p>Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.</p>

Date	SmPCs introduced
	<p>Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.</p> <p><i>Developmental disorders</i></p> <p>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.</p> <p>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.</p> <p>Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.</p> <p>There are limited data on the long term outcomes.</p> <p>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.</p> <p>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><i>Female children and woman of childbearing potential (see above and section 4.4)</i></p> <p><i>If a woman plans a pregnancy</i></p> <p>If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.</p>

Date	SmPCs introduced
	<p data-bbox="492 323 695 352"><i>Pregnant women</i></p> <p data-bbox="492 359 1404 495">Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.</p> <p data-bbox="492 537 1404 814">All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</p> <p data-bbox="492 856 719 886"><u>Risk in the neonate</u></p> <ul data-bbox="492 892 1404 1535" style="list-style-type: none"> <li data-bbox="492 892 1404 1209">• Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.</li> <li data-bbox="492 1215 1404 1283">• Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.</li> <li data-bbox="492 1289 1404 1356">• Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.</li> <li data-bbox="492 1362 1404 1535">• Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.</li> </ul> <p data-bbox="492 1577 667 1606"><u>Breast-feeding</u></p> <p data-bbox="492 1612 1404 1711">Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).</p> <p data-bbox="492 1753 1404 1852">A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.</p>

Date	SmPCs introduced
	<p><u>Fertility</u> Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.</p> <p>Section 4.8 Undesirable Effects Congenital malformations and developmental disorders (see section 4.4 and section 4.6).</p>
2018	<p><b><u>Added Oestrogen warning to already existing text</u></b></p> <p>Section 4.4 <u>Oestrogen-containing products</u> Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products. On the opposite, valproate does not reduce efficacy of hormonal contraceptives.</p> <p>Section 4.5 <b><i>Oestrogen-containing products, including oestrogen-containing hormonal contraceptives</i></b> Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels. On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.</p> <p>Section 4.6 <u>Oestrogen-containing products</u> Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).</p>



**(G) WHETHER ANY STATUS OTHER THAN PRESCRIPTION ONLY MEDICINE HAS BEEN SOUGHT**

Epilim and Depakote have always been prescription only medicines and no application to change this status has ever been made.

**(H) ANY NATIONAL RESTRICTIONS ON PRESCRIBERS OR PRESCRIBING (WITH DATES) THAT YOU ARE AWARE OF**

Sanofi are not aware of any restrictions on prescribers or prescribing other than those laid out in the marketing authorisation.



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### Response to Question 3

**For each medication please can you include copies of data sheets, product labels and timelines indicating any change in the product labels.**

The list of datasheets /summaries of product characteristics (SmPCs) and Patient Information Leaflets or product labels (PILs) provided with this response are listed below. Copies of each document can be found in the Annex to this submission. A timeline in terms of how the content of the datasheet/ SmPC has changed over time is provided in the response for Question 2.

#### Epilim

The information is provided for Epilim 200mg enteric coated tablet, which is representative of the information provided across the range of valproate products.

For 1975 through to 2000, information is provided to the Review as presented in the published Datasheet Compendia, which were published on an annual basis. They therefore present a “snapshot” in time. When information was updated between the annual printed versions of the Compendia, then this was available to HCPs on request from the Company.

For the period from 2000 onwards, copies of all those SmPCs where there have been updates to the information related to women of childbearing potential and pregnancy are provided.

Submission Date	Approval Date	Document Description	Document Name
1975 – 2000	1975 – 2000	Full printed datasheets	Photocopy from Datasheet Compendium provided and copies of PILs for 1989, 1994, 1996, 1997 & 1998
14 December 2000	26 March 2001	Global update - To update clinical particulars (sec 4.1 to 4.9) in line with current safety information to ensure consistency of prescribing information across the product range and include warnings regarding sodium valproate and pancreatitis. Other formal changes and reformatting changes in line with SPC guideline. <i>(pregnancy related changes)</i>	2001 03 SPC 2001 03 PIL
09 January 2003	17 April 2003	Requested by MHRA - updated sec 4.4 (women of child bearing....) and 4.6 (risk associated with epilepsy....) <i>(pregnancy related changes)</i>	2003 04 SPC 2003 11 PIL

Submission Date	Approval Date	Document Description	Document Name
19 November 2004	18 October 2005	Safety update version 9 (updated sections 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1) ( <i>pregnancy related changes</i> )	2005 10 SPC 2005 10 PIL
23 April 2009	17 May 2010	Safety update version 10, 11 - To update sec 4.4 to include special warnings for women of child bearing potential	2010 10 SPC 2010 10 PIL
23 April 2009	01 October 2010	Safety update version 10, 11, 12 - To update sec 4.6 ( <i>pregnancy related changes</i> )	2010 10 SPC 2010 10 PIL
07 June 2011	13 July 2011	Safety update version 13 (updated sec 4.4, 4.5, 4.6, 4.8) ( <i>pregnancy related changes</i> )	2011 07 SPC 2011 07 PIL
24 August 2012	28 November 2012	Safety update version 14 (updated sec 4.6, 4.8) ( <i>pregnancy related changes</i> )	2012 11 SPC 2012 11 PIL
07 January 2015	11 February 2015	Safety update PRAC review- updated sec 4.2 (posology) 4.4 (text box) and 4.6 (re arranged the text and remove seizures) ( <i>pregnancy related changes</i> )	2015 02 SPC 2015 02 PIL
31 January 2018	31 August 2018	Safety update version 23 (updated sec 4.4, 4.5, 4.6, 4.8, 5.2) with warning for 'oestrogen containing product'.	2018 08 SPC 2018 08 PIL
22 March 2018	30 April 2018	Safety update PRAC review (updated sec 4.2, 4.3, 4.4 (sec re arranged in sub categories), 4.6) ( <i>pregnancy related changes</i> )	2018 04 SPC 2018 04 PIL



## Depakote

The information is provided for the 250mg tablets. The same information is approved for the Depakote 500mg tablets.

Submission Date	Approval Date	Document Description	Document Name
	21 December 2000	Initial Marketing Authorisation granted – First registered SmPC and PIL	2000 12 SPC 2000 12 PIL
09 January 2003	17 April 2003	Requested by MHRA - updated sec 4.4 (women of child bearing....) and 4.6 (risk associated with epilepsy....) ( <i>pregnancy related changes</i> )	2003 04 SPC 2003 10 PIL
14 April 2004	12 May 2004	Safety update (update section 4.6) ( <i>pregnancy related changes</i> )	2004 05 SPC 2003 10 PIL
19 November 2004	27 September 2005	Safety update version 9 (updated sections 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1) ( <i>pregnancy related changes</i> )	2005 09 SPC 2005 09 PIL
23 April 2009	19 May 2010	Safety update version 10, 11 - To update sec 4.4 to include special warnings for women of child bearing potential	2010 09 SPC 2010 09 PIL
23 April 2009	16 September 2010	Safety update version 10, 11, 12 - To update sec 4.6 ( <i>pregnancy related changes</i> )	2010 09 SPC 2010 09 PIL
12 November 2010	12 November 2010	Safety update version 13 (updated sec 4.1, 4.2, 4.4, 4.6) – Article 31 bipolar disorder ( <i>pregnancy related changes</i> )	2010 11 SPC 2010 11 PIL
07 June 2011	13 July 2011	Safety update version 13 (updated sec 4.4, 4.5, 4.6, 4.8) ( <i>pregnancy related changes</i> )	2011 07 SPC 2011 07 PIL

Submission Date	Approval Date	Document Description	Document Name
24 August 2012	28 November 2012	Safety update version 14 (updated sec 4.6, 4.8) ( <i>pregnancy related changes</i> )	2012 11 SPC 2012 11 PIL
08 January 2015	05 February 2015	Safety update PRAC review- updated sec 4.2 (posology) 4.4 (text box) and 4.6 (re arranged the text and remove seizures) ( <i>pregnancy related changes</i> )	2015 02 SPC 2015 03 PIL
31 January 2018	31 August 2018	Safety update version 23 (updated sec 4.4, 4.5, 4.6, 4.8, 5.2) with warning for 'oestrogen containing product'.	2018 08 SPC 2018 08 PIL
22 March 2018	30 April 2018	Safety update PRAC review (updated sec 4.2, 4.3, 4.4 (sec re arranged in sub categories), 4.6) ( <i>pregnancy related changes</i> )	2018 04 SPC 2018 04 PIL



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## Response to Question 4

### Please can you provide sales data for each medication, and if known, market share for the lifespan of the product.

IQVIA, a well-respected industry market analysis organisation, provides IMS market and sales data for the past 5 years. Sanofi has used these data as the basis for this response.

#### **Sanofi branded valproate-based medicines:**

Sanofi currently has two branded valproate-based medicines licensed for the UK market

- Epilim (sodium valproate and valproic acid) for the treatment of epilepsy
- Depakote (semi-sodium valproate) for the treatment of bipolar disorder.

#### Epilim (sodium valproate and valproic acid):

Over the past 5 years there has been a decline in valproate use (comprising all valproate-based medicines) within the valproate market share of the epilepsy market reducing from 12.1% to 9.1% (N03A0 ATC4<sup>1</sup> class, IMS Aug 2018).

The N03A0 ATC4 class comprises preparations used in the treatment of epilepsy and is therefore the most appropriate class to review for this market. However, many medicines within the Central Nervous System (CNS) market are used for multiple indications, which makes demonstrating trends challenging and must be taken into consideration when analysing the data. What it shows, is that the usage trend for valproate is decreasing.

At present there are over 110,400 patients taking Epilim. Over the past 5 years the number of women of childbearing potential taking Epilim has reduced by 9.0% from 17,172 to 15,633 (14% of total Epilim volume) (IMS Aug 2018). The number of female children taking Epilim has reduced by 36.8% from 3,271 to 2,068 (1.9% of total Epilim volume) (IMS Aug 2018).

Valproate is a highly effective drug for the treatment of generalised and partial epilepsies, and for some patients, suffering from certain forms of resistant epilepsies, including some women of child-bearing potential and some girls, it remains the only effective therapeutic option

#### Depakote (semi-sodium valproate):

Over the past 5 years the Depakote share of the bipolar market has declined from 4.1% to 3.5% (N06A3 + N05A1 ATC4 class, IMS Aug 2018).

At present there are over 25,500 patients taking Depakote. Over the past 5 years the number of women of childbearing potential taking Depakote has reduced by 38.8% from 8,177 to 5,002 (19.5% of total Depakote volume). (IMS Aug 2018).

Sanofi does not have information on the sales data for the full lifespan of each medication.

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<sup>1</sup> **Anatomical Therapeutic Chemical Classification System**, a system of alphanumeric codes developed by the WHO for the classification of drugs and other medical products



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## **Response to Question 5**

**If known, could you also provide information on what proportion of valproate medication sales are for off label usage.**

Sanofi is fully committed to complying with the requirements of the Human Medicines Regulations 2012 and the ABPI Code of Practice and, as such, does not support or encourage use of valproate outside its licensed indications. Sanofi is not aware of the proportion of off-label use of either Epilim or Depakote as individual Sanofi products, nor the valproate market in its entirety. Sanofi is therefore unable to provide an answer to this question.



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## Response to Question 6

### **Please share any evidence of positive feedback on valproate containing medications for women of child bearing age from clinicians or patient groups.**

Epilim (valproate) is indicated for “for the treatment of generalised, partial or other epilepsy” in both men and women. Any consideration of use of the product in Women of Childbearing Potential (WOCBP) must therefore also take into account the benefits of use in men and in women who are not WOCBP. It remains one of the most effective treatments in generalised epilepsy and for some patients suffering from certain resistant epilepsies, it is the only treatment to provide adequate seizure control.

Valproate is an important treatment that thousands of men and women in the UK continue to rely on to control seizures during their lifetime. The health risks from poor control of seizures should not be underestimated. The appropriate specialist review of patients with epilepsy and the information available to prescribers and patients in product information and in guidance such as that issued by NICE are intended to ensure that anti-epileptic drugs, including valproate, are used appropriately.

### **The World Health Organisation (WHO) lists valproate as an essential medicine**

The World Health Organisation (WHO) recognises valproate as an essential medicine and the product is included on their Core List. They define the Core List as a “*list of minimum medicine needs for a basic health - care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost effective treatment*”<sup>i</sup>.

### **Statements by medical experts in relation to use of valproate in WOCBP**

Sanofi has set out below some quotations from statements by medical experts and national guidance on the use of valproate in WOCBP. It is not an exhaustive list and should not be treated as such, but rather be illustrative of the views of certain neurologists explaining their reasons for recommending use of valproate in some WOCBP.

#### **Martin Brodie, President of International Bureau for Epilepsy (IBE), Director of Epilepsy Unit, Western Infirmary, Glasgow:**

On 26 September 2017, Martin Brodie provided evidence to the European Medicines Agency’s (EMA) pharmacovigilance risk assessment committee (PRAC) review of the safety of using valproate-containing medicines in women and girls who are pregnant or of childbearing age. He stated:

*“VPA [valproate] was licensed for the treatment of epilepsy in 1967 and is also widely used for bipolar disorder and migraine. It is widely regarded as the drug of choice for the idiopathic generalized epilepsies and is also frequently prescribed for focal epilepsies with or without secondary generalization. VPA has been recognised as teratogen for many years, as have other antiepileptic drugs, such as phenobarbital and topiramate. Like all these agents, the teratogenicity of VPA is known to be dose dependent with a substantially reduced risk at doses of 500-700 mg daily, which can be therapeutic in some patients with newly diagnosed epilepsy. There is also the potential of using low dose VPA with lamotrigine, which is the only proven synergistic combination of antiepileptic drugs.*

*Uncontrolled epilepsy, particularly in young people, carries a risk of sudden unexpected death (SUDEP) and so leaving seizures, especially tonic-clonic seizures, uncontrolled is not an acceptable option. I have patients, particularly those with idiopathic generalized epilepsy, for whom VPA proved to be the only*

*successful treatment. We accept the need to restrict its use in young women, but would support its prescription as a drug of last choice, if all other approaches prove unsuccessful. In addition, there are many women who do not have pregnancy in their life plan. Both these categories of patient should have the option of taking VPA after careful, accurate and sensitive explanation of the risk-benefit ratio to all concerned. VPA is an effective and well tested antiepileptic drug that should not be discarded as a therapeutic choice for every young woman with epilepsy”<sup>ii</sup>.*

Helen Cross, Coordinator for European Reference Network for Epilepsy (EpiCARE), The Prince of Wales’ Chair of Childhood Epilepsy and Head of University College London-Institute of Child Health Neuroscience Unit:

On 26 September 2017, Helen Cross provided evidence to the EMA’s PRAC review of the safety of using valproate-containing medicines in women and girls who are pregnant or of childbearing age. She stated:

*“We recognise and acknowledge that use of valproate during pregnancy poses a significant risk of harm to the unborn child. However, sodium valproate remains an extremely useful antiepileptic medication, of considerable benefit in some of the rare and complex epilepsies. Although we acknowledge that this hearing is to address actions put in place to minimise the risks of valproate in women who are pregnant or of childbearing age, our concern is that such measures may hinder use in individuals with these rare epilepsies and therefore compromise seizure control and quality of life. Many of these individuals have severe learning disability, and risk-benefit of use of the medication needs to be considered. We ask that use in individuals with rare epilepsies such as Dravet syndrome and others may require different consideration, particularly as approaching child bearing age, as use of the medication may offer greater benefit than risk”<sup>iii</sup>*

Sanjay Sisodiya, Director of Genomics, Epilepsy Society (UK). Professor of Neurology, University College London (UCL):

On 26 September 2017 Sanjay Sisodiya provided evidence to the EMA’s PRAC review of the safety of using valproate-containing medicines in women and girls who are pregnant or of childbearing age. He said:

*“For those with idiopathic generalised epilepsy, sodium valproate (SVA) can be one of the most effective treatments in all seizure types (absence, myoclonus and tonic clonic). However, due to its teratogenicity, SVA should be avoided, where possible, as a first line treatment in girls and women of childbearing age. Up to 40 per cent of babies exposed to SVA in the womb are at risk of developmental disorders, and up to 10 per cent are at risk of birth defects such as spina bifida or cleft palate. However for some girls and women, SVA may be the only drug that will control their seizures, and seizures are not benign events. In some circumstances, tonic clonic seizures may cause miscarriage, trauma related to falls and blood conditions that can affect the developing baby - such as foetal hypoxia. The risk of SVA has to be assessed against the risk of seizures to both mother and baby”<sup>iv</sup>.*

#### **Guidance issued by the National Institute for Health and Care Excellence (NICE)**

NICE guidance on ‘Epilepsies: diagnosis and management (CG137)’, published in January 2012 and updated in April 2018, states that:

*“Newer and more expensive AEDs are now being prescribed, and with an increase in treatment costs likely in coming years it is essential to ensure that AEDs with proven clinical and cost effectiveness are identified. The evidence used to develop the previous NICE guideline for epilepsy and related technology appraisals showed no difference in effectiveness between newer and older AEDs, or between the newer drugs (as monotherapy) for seizure control. However, a recent large multicentre trial (the SANAD trial) evaluating newer drugs in newly diagnosed epilepsy (accepting some limitations) suggested that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in focal epilepsies. It was therefore considered necessary to review new evidence regarding AEDs within an*

update of NICE clinical guideline 20 (which was published in 2004)”<sup>v</sup>.

It also states:

P27:

- *“Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed generalised tonic-clonic (GTC) seizures. Follow the MHRA safety advice on sodium valproate”*.
- *“Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence seizures. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Follow the MHRA safety advice on sodium valproate. [2018]”*

Pg. 28:

*“Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed myoclonic seizures, unless it is unsuitable. Follow the MHRA safety advice on sodium valproate. [2018]”*

Pg. 29:

*“Offer sodium valproate as first-line treatment to children, young people and adults with tonic or atonic seizures. Follow the MHRA safety advice on sodium valproate. [2018]”<sup>vi</sup>*

Pg. 32:

*“Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed IGE, particularly if there is a photoparoxysmal response on EEG. Follow the MHRA safety advice on sodium valproate [2018]”*.

Pg. 33:

*“Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed [juvenile myoclonic epilepsy], unless it is unsuitable. Follow the MHRA safety advice on sodium valproate [2018]”*.

Pg. 34:

*“Offer lamotrigine or sodium valproate as first-line treatment to children, young people and adults with epilepsy with GTC seizures only. If they have suspected myoclonic seizures, or are suspected of having JME, offer sodium valproate first, unless it is unsuitable. Follow the MHRA safety advice on sodium valproate [2018]”*.

Pg. 35:

*“Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence syndromes. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Follow the MHRA safety advice on sodium valproate [2018]”*.

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<sup>i</sup> WHO Model List of Essential Medicines. 20th List (March 2017) (Amended August 2017). p6.

<http://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1><http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf?ua=1>

<sup>ii</sup> European Medicines Agency. Public Hearing on Valproate. Written Interventions. 2 October 2017. Martin Brodie, International Bureau of Epilepsy. [https://www.ema.europa.eu/documents/other/public-hearing-valproate-written-interventions\\_en.pdf](https://www.ema.europa.eu/documents/other/public-hearing-valproate-written-interventions_en.pdf), p18.

<sup>iii</sup> *Ibid.* Helen Cross, European Reference Network for Epilepsy, p34.

<sup>iv</sup> *Ibid.* Sanjay Sisodiya, Epilepsy Society, p40

<sup>v</sup> National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management (CG137. Clinical guideline Published: 11 January 2012. p9. <https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-pdf-35109515407813>

<sup>vi</sup> *Ibid.* p27, p28, 29.



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## Response to Question 7

### Please can you supply a summary of adverse event reports related to valproate use in pregnancy, with dates of receipt but fully anonymised. How have you responded to these?

Sanofi is committed to the continuous monitoring of the use of its medicines in the post approval environment in order to ensure such products are used as safely as possible.

#### Introduction

1. The regulatory requirements and practice in relation to the reporting of adverse effects to the regulatory authorities (including the types of adverse effects that should be reported) and pharmacovigilance activities generally, have evolved very substantially during the period since 1973, when valproate products were first supplied in the UK. In 1973, pharmacovigilance was a relatively new discipline and measures concerned with drug safety were comparatively less developed than nowadays. Today, however, regulatory requirements are extensive and pharmacovigilance systems, including those operated by Sanofi, are highly sophisticated, assisted by advances in technology which support collection and analysis of reports in global electronic databases. The development of regulatory requirements, covering the relevant period, is described in the response to Q13.
2. Up until the mid-1990s, the pharmacovigilance system at Sanofi in the UK was a mixture of paper based records and a simple electronic database for recording suspected adverse drug reactions ("ADRs"). From the early 1980s ADRs have been collected from all countries where the product was marketed. A central computerised database was set up in 1991.

#### Interpretation of reports

3. The fact of a report of an adverse event experienced following exposure to a medicinal product does not mean that the relationship is causal. The interpretation of reports of suspected ADRs (including abnormal pregnancy outcomes) may be challenging. In particular, determining whether any association between exposure to the relevant medicinal products and the adverse event experienced by the patient is causal, can be a difficult and inconclusive process, as the assessment may be confounded by exposure to concomitant diseases, environmental factors and other medicines. In the case of pregnancy outcomes, there are multiple potential confounding factors to be considered, including the parental medical history (both paternal and maternal), genetic antecedents, perinatal factors and environmental exposures affecting parents and child.
4. The investigation of causality is even more difficult where the suspected ADR is identified some time after the exposure (as is the case with reports of developmental delay or autism spectrum disorder (ASD) in children who were exposed to valproate in utero), where multiple factors following the exposure may be relevant to the adverse event.
5. The Marketing Authorisation Holder (MAH) and the health authorities have a cumulative dataset which allows for aggregate analysis and enables them to share the analysis of this data.

#### Reports relating to use in pregnancy provided to the UK regulatory authorities

6. All received pregnancy reports were reviewed by the MAH. There were no regulatory requirements for expedited reporting of such reports unless these involved a serious suspected adverse drug



reaction. Sanofi was, in any event, concerned to collect all available information in relation to use of valproate during pregnancy and would therefore follow up any cases of pregnancy in patients who were prescribed valproate which became known to the company. Efforts were made in accordance with Sanofi's procedures, to investigate all notified pregnancies (generally, several letters would be sent to the treating doctor enclosing a specific form) in order to confirm the outcome. However, despite these efforts, relatively few responses were received by the company.

7. So far as Sanofi is aware all abnormal pregnancy outcomes were reported by Reckitt-Labaz to the regulatory authority from the time of first marketing of Epilim in the UK. From 1981, when Sanofi became responsible for Epilim in the UK, the company has reported all abnormal pregnancy outcomes to the UK Regulatory Authority. From 1997 all evidence available to Sanofi regarding exposure to valproate during pregnancy and outcomes (i.e. including "normal" outcomes) has been provided to the UK Regulatory Authority in Periodic Safety Update Reports (PSURs).

#### **Summary of worldwide adverse event reports related to pregnancy outcomes following valproate use**

8. In responding to the question posed by the Review, we rely principally on the cumulative data collected on pregnancy outcomes and presented in PSURs from 1997. Prior to 1997, periodic reports reflected only the specific period to which they related and did not include cumulative review on pregnancy outcomes as such review was not required by the regulations and industry standards. Cumulative reviews were performed on worldwide data because the assessment of safety signals is based on worldwide information rather than reports from a single country. We have specifically searched the several cumulative reviews relating to pregnancy outcomes as described below. Such documentation reflects the data available with the methodology used at that time.
9. In considering the data, it is relevant to take into account the fact that medical descriptions and terminology have changed over the years covered by the request and this impacts the information provided. In particular, there was no standard search methodology and terminology covering symptoms encompassed by "neurodevelopmental delay". It should also be noted that a new medical dictionary (MedDRA) on the definition of medical terms used to code the adverse reactions in the Sanofi global database has been implemented in April 2002, replacing the former dictionary (WhoART). The conundrum of the lack of standard search methodology persists today because the term "neurodevelopmental delay" is an umbrella term which covers different types of disorders. Furthermore, the medical dictionary relied upon for search terms also evolved during the period, with new terms being added. Since 1991, search terms and methodology for investigating reports of neurodevelopmental delay have evolved and changed. Therefore outcomes of database searches in this area are not directly comparable between different time periods.
10. Furthermore, over time, requirements for data exchange agreements between companies have been introduced and these have resulted in more cases being exchanged and reported into the Global Database. Such data exchange contributed to the cumulative increase in the number cases in later years.
11. Seven extracts are presented below to illustrate the evolution of cumulative knowledge based on documents submitted to the health authorities. They were extracted from the following documents:
  - (a) The Periodic Safety Update Report (PSUR) covering the period from 1 February 1997 to 31 December 1999 on neurodevelopmental delay; (The PSUR was sent to the Health Authorities in all EU member states, in accordance with regulatory requirement);
  - (b) A summary report written in 2004 as submitted to the MHRA to update the Summary of Product Characteristics (SmPC) in relation to neurodevelopmental delay;

- (c) Cumulative review on Autism, Autism Spectrum Disorders (ASD) and Asperger's syndrome in the PSUR (data lock point 31 January 2006);
- (d) A summary report written in 2008 as submitted to the MHRA in relation to autism, autism spectrum disorders and Asperger's syndrome;

- [REDACTED]
- (f) PRAC assessment report in 2014, as written by the rapporteurs, related to the Article 31 Referral, on congenital anomalies and developmental issues;

12. The contents of the above datasets are described in more detail below.

**(a) PSUR: 1 February 1997 - 31 December 1999: neurodevelopmental delay**

The first PSUR covered the period from the 1st February 1997 to the 31st December 1999. As the terms "congenital malformations"/"congenital abnormalities" were already listed in the Company Core Safety Information (CCSI) and the UK SmPC, no cumulative review on this topic was performed, in accordance with the PSUR requirement which did not include the presentation of cumulative data of a listed reaction. Notwithstanding this, the MAH continued to monitor and report information on congenital malformation to the Health Authority.

This was the first time that a cumulative review was performed on reports of suspected ADRs coded "psychomotor development impaired, growth retardation, foetal maturation impaired, mental deficiency, or thinking abnormal" following exposure to valproate in utero, from the commencement of the Global Electronic Pharmacovigilance Database in 1991 up to 31 December 1999.

All the relevant reports related to "impaired psychomotor development" that were retrieved from the Sanofi Global PV database were included in the worldwide cumulative review. These included reports from Healthcare Professionals, Health Authorities and those in the scientific literature.

Incomplete information was received in every case: missing delivery condition, long term follow-up of children, consideration of malformation, mother's seizure type and severity, seizure controls, parental educational level, psychosocial factors.

The conclusion of the above PSUR was the following: "*From the data presented in this safety update, the cumulative experience to date and literature, a new area of interest has been identified namely development delay. Based on current information no definite relationship can be established between valproate and development delay in children exposed in utero to valproate. Nevertheless, this topic will remain under surveillance*".

Please refer to Response to Question 9 for additional details.

Such cumulative review was performed regularly and reported in the PSURs submitted to the health authority in compliance with regulatory requirements and industry standards.

**(b) A summary report written in 2004 and submitted to the MHRA to update the SmPC in relation to neurodevelopmental delay**

In 2004, a summary of safety data was submitted to the regulatory authority in support of an application to update the information provided in the SmPC for Epilim in relation to neurodevelopmental delay. The summary stated the following: "Some data have suggested an association between in-utero VPA exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ".

A review of available information on developmental delay following in utero exposure to valproate was performed. This review included a cumulative analysis of all adverse reactions related to "developmental delay" reported in children exposed in utero to valproate, from the commencement of Sanofi's Global Electronic Pharmacovigilance Database up to 31 January 2004.

All the relevant reports that were retrieved from the Sanofi Global PV database were included in the worldwide cumulative review. These included reports from Healthcare Professionals, Health Authorities and those in the scientific literature. Causality assessment of these cases was difficult as information was incomplete and many reports were poorly documented. By way of example, some cases with minimal information were received from the same reporter who may have been involved in a retrospective study of children born to mothers with epilepsy. In other cases confounding factors were present.

Although the causality assessment of many of such ADRs was inconclusive, Sanofi requested that this information be included, as a matter of caution, in the SmPC and PIL for the product (please refer to Response to Question 9 for additional details).

**(c) Cumulative review in the PSUR (data lock point 31 January 2006): Autism, Autism Spectrum Disorder (ASD) and Asperger's syndrome**

In the above-mentioned PSUR, a cumulative review on autism, autism spectrum disorders (ASD) and Asperger's syndrome was performed. All the relevant reports that were retrieved from the Sanofi Global PV database were included in the worldwide cumulative review. These included reports from Healthcare Professionals, Health Authorities and those in the scientific literature.

The conclusion of the review was the following: "According to the National Center for Health Statistics, the prevalence of autism ranges from a round 10 to 15 cases per 10, 000 populations. It is noteworthy that a statement is present in the CSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient (IQ). No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company."

**(d) A summary report written in 2008 and submitted to the MHRA in relation to autism, ASD and Asperger's syndrome**

A clinical review was written in 2008 to support Sanofi's applications to the MHRA to amend the SmPC for Epilim to add information on autism in the section "pregnancy". All the relevant reports that were retrieved from the Sanofi Global PV database were included in the worldwide cumulative review. These included reports from Healthcare Professionals, Health Authorities and those in the scientific literature.



The conclusion of the summary report, including medically confirmed cases recorded in the Sanofi database and literature, was as follows: "In conclusion, data are available on autism in children after maternal exposure to valproate, but there is currently limited information on this causal relationship. The company proposes to mention such a safety signal in the section "Pregnancy" of the CCSI for valproate".

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]

(f) **PRAC assessment report in 2014 related to the Article 31 Referral: congenital anomalies and developmental issues**

The referral under Article 31 of Directive 2001/83/EC in 2014, was referred to and assessed by the PRAC (PRAC referral assessment report EMA/PRAC/16647/2014).

In its assessment, the PRAC considered all the data submitted in relation to the safety of valproate in female children, women of childbearing potential and pregnant women from different sources. For this purpose, Sanofi submitted a review of cases reported after exposure in utero to valproate that had been entered in the Global Electronic Pharmacovigilance Database up to 31 October 2013.

A total of 2958 cases of in utero exposure to valproate or valpromide were retrieved from the Sanofi Global Electronic Pharmacovigilance Database.

**Exposure**

The majority of the cases arose from the use of valproate for the treatment of epilepsy (53.1% (1570/2958)) followed by 5.5% (162/2958) of cases in bipolar disorder. The indication was unknown in 39% of the cases. This illustrates the point that, in the post-marketing setting, the MAH's analysis is often constrained by the quality of information provided in case reports.

Of the total cases of exposure, 424 cases were reported in both sub-groups 'Congenital familial and genetic disorders' and 'Impaired cognitive development'. 14% of the cases described coexisting diseases that could have confounded the impaired cognitive development (61/424). These conditions were mainly structural brain disease and deafness.

**Pregnancy outcome**

**i. Congenital anomaly cases**

A total of 1750 cases of congenital malformation out of the 2958 cases of exposure in utero with valproate and valpromide were identified in the MAH's pharmacovigilance database. Of these cases of congenital malformation, the main indications were epilepsy in 58% and unknown in 39% of cases. The cases were mainly distributed in the following secondary System Organ Class (SOCs):

- Musculoskeletal and connective tissue disorders (675/1750, 39% of all cases) with the most frequently reported Preferred Terms (PTs) related to dysmorphism, polydactyly / arachnodactyly / brachydactyly / syndactyly / macrodactyly, limb / hand / foot malformation, microcephaly / macrocephaly / brachycephaly / scaphocephaly / plagiocephaly.
- Nervous system disorders (621/1750, 36% of all cases) – the most frequently reported PT was 'spina bifida'.

- Cardiac disorders (414/1750, 23% of all cases) – the most frequently reported PTs related to atrial/ventricular septal defect, congenital heart disease NOS and congenital cardiovascular anomaly NOS.
- Pregnancy, puerperium and perinatal conditions (398/1750, 23% of all cases) – the most frequently reported PTs related to foetal anticonvulsant syndrome.

The MAH reported that the period of exposure during pregnancy was unknown for the majority of cases (1217/1750, 70% of all cases). Across all indications, 30% (518/1750) of cases were treated with valproate/valpromide during at least the first trimester of pregnancy. One fifth of all cases (21%, 359/1750) involved exposure during the entire pregnancy. Of patients with epilepsy, 32% (328/1017) received treatment during the entire pregnancy. The daily dose was unknown in the majority of cases (59%, 1023/1750). When reported, patients were most frequently prescribed 1000-1500mg/day (33% of cases with dose reported, 243/727), or 700- 1000mg/day (32%, 231/727). Only 4% of patients received >2500mg/day (29/727).

It is to be noted that the product information of valproate and related substances recommends a maximum daily dose of 2500mg/day and states that most patients achieve seizure control with a daily dose of 1000-2000mg/day.

ii. Impaired cognitive development cases (including autism, ASD and ADHD)

Paragraphs (a) to (d) set out above, separated the analysis of developmental delay and autism. In contrast, the PRAC assessment report grouped these together into a single category. As a result, 699 cases of impaired cognitive development were identified. These cases included 106 cases of autism and ASD, as well as the 21 cases of ADHD (which are described below), as submitted by the MAH to the PRAC for the purposes of the Article 31 referral.

iii. ADHD and motor developmental delay cases

21 cases with a diagnosis of ADHD after in utero exposure to valproate were identified from the Sanofi Global Electronic Pharmacovigilance Database.

132 cases of motor developmental delay after in utero exposure to valproate were also identified.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Sanofi's response to reports of adverse events following use in pregnancy**

13. All safety related information, including use during pregnancy received from healthcare professionals, patients, consumers or other sources forms part of Sanofi's pharmacovigilance activity for all its medicines in the post authorisation environment.
14. These activities including signal detection and assessment, labelling update, risk minimisation activities are described in the responses to Q11-12, Q13. Further information is provided in the response to Q9.



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## Response to Question 8

### **Do you have any ongoing post-marketing studies of relevance to the Review? If so, please provide details.**

One post authorisation safety study that was required following the outcome of the Article 31 referral in 2014 and one local study in France are ongoing at the present time:

- A joint drug utilisation study of valproate and related substances in Europe using databases, with the objective of assessing the effectiveness of various risk minimisation measures. As required by the EMA guidelines, the study information is available on the ENCEPP register (register number EUPAS9678).
- A survey of pharmacists in order to assess French minimization measures on prescribing and delivery compliance (PDC) of valproate in dispensing pharmacies.

As required by the outcome of the Article 31 referral of 2017, the following joint studies, to be conducted with the marketing authorisation holders of other valproate products, are currently in their planning phase and protocols will be submitted in accordance with Article 107n (1) of Directive 2001/83/EC by November 2018:

- A drug utilisation study extension to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate.
- An observational study to evaluate and identify the best practices for switching patients from treatment with valproate to alternative therapies, in clinical practice.
- A survey among HCPs to assess knowledge of HCPs and behaviour with regard to the pregnancy prevention program as well as receipt/use of DHPC and educational materials.
- A survey among patients to assess knowledge of the patients with regard to the pregnancy prevention program as well as receipt/use of educational materials.
- A retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in their offspring.



## Response to Question 9

**Please could you provide a timeline outlining your understanding of and recognition of risks regarding the use of valproate in pregnancy. This may include: initial recognition of the risks, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.**

1967	<p>Discovered to have anti-epileptic properties in 1962 by Laboratoires Berthier (“LB”) and subsequently investigated as an anticonvulsant, Sodium valproate was initially licensed in France with the approved therapeutic indications of: (a) generalised or focalised epilepsies and (b) personality or character disorders linked to epilepsy.</p> <p>The product was introduced onto the French market.</p>
1969	<p>Sodium valproate supply was commenced in Belgium, Holland, Luxembourg, West Germany and Spain, through a licensing agreement with Belgian company, Labaz.</p>
	<p>Further clinical trials carried out in the UK confirmed that sodium valproate was effective in reducing the incidence of seizures in patients with petit mal, grand mal, myoclonic and akinetic epilepsy and photosensitive epilepsy, including in patients with long standing epilepsy that had proved refractory to other therapies.</p>
	<p>An enteric coated formulation of sodium valproate was developed to reduce the incidence of gastro intestinal symptoms (indigestion, heartburn and nausea) associated with oral administration.</p>
2 August 1972	<p>The UK licensing authority (Ministers) granted a conditional product licence for sodium valproate 200mg plain tablets, under the brand name “Labazene” (changed to “Epilim” on March 1973) to Pharmacy Products (UK) Limited, a joint venture between Labaz Group and Reckitt &amp; Colman (“R&amp;C”). The licence was limited to a period of one year and was subject to the condition that all patients would be monitored for efficacy and safety and the results reported to the licensing authority in writing at six months and, again, at ten months after grant of the licence.</p>
March 1973	<p>Commencement of supply of Epilim in the UK</p>
September 1973	<p>Pharmacy Products (UK) Limited applied for a full UK product licence for sodium valproate. At that time, the product had been marketed in five European countries for up to four years and no reports of congenital abnormalities in infants exposed to the product during pregnancy had been received.</p>
28 October 1974	<p>A full licence was issued for five years commencing 2 August 1973. In light of animal data in relation to teratogenic effects, the licence was subject to conditions imposed</p>

	<p>by the licensing authority, including the requirement to set out the following wording in the data sheet and in any materials promoting the product to doctors:</p> <p><i>“(a) Under “Uses” the licence shall read “for use in generalised focal or other epilepsy. In women of child bearing age, the product should only be used in severe cases or those resistant to other treatment”.</i></p> <p><i>(b) The following warning shall be included in the data sheet and in all promotional material for this product (i.e. mailings, journal advertisements, literature handed out by representatives etc.):-</i></p> <p><i>“Women of childbearing age</i></p> <p><i>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.”</i>”</p>
1981	<p>Sanofi acquired the Labaz Group. At that time, three formulations of Epilim were licenced in the UK: Epilim Plain Tablets 200mg, Epilim Enteric Coated (200mg and 500mg) and Epilim Syrup.</p> <p>At the time, the data sheets for Epilim included the limitation on use by women of child-bearing age and the warning regarding the potential implications of the results of the tests conducted in animals, directed by the licensing authority in 1974. These reflected the teratogenic effects of sodium valproate seen in animal studies:</p> <p><b><i>“Uses</i></b></p> <p><i>In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, Epilim should be used only in severe cases or those resistant to other treatment.”</i></p> <p><b><i>“Contra-indications, warnings, etc...”</i></b></p> <p><i>Women of child-bearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have 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.”</i></p> <p>This wording reflected the state of scientific knowledge at the time. Indeed, in 1980, a collaborative study group in Japan reported its finding that a number of anti-epileptic drugs, including phenobarbital and primidone, induced significant teratology, although the teratogenic effects of sodium valproate (and phenytoin and carbamazepine) failed to reach significant levels.<sup>1</sup> The authors concluded:</p> <p><i>“One of the aims of this study is to answer the question of the safety, teratologically speaking of the antiepileptic drugs. Our feelings are that the teratogenicity of these drugs, except for TMO [trimethadone], is not high. Although barbiturates and their</i></p>

<sup>1</sup> Nakane et al. Multi-institutional study on the teratogenicity and foetal toxicity of antiepileptic drugs: A report of a collaborative study group in Japan. *Epilepsia* 1980; 21: 663-680

	<p><i>derivatives may present some significant risks, PHT [phenytoin] does not. While teratogenic effects must be emphasised as our first concern, we also need to focus our attention on developing the safest regimens possible for those who must continue on medication during pregnancy”.</i></p>
August 1981	<p>An article in the British Medical Journal (the “BMJ”) concluded that</p> <p><i>“...on balance, although phenytoin and other antiepileptic drugs appear to carry a teratogenic risk, it does not justify (with the exception of the diones) discouraging a women who needs anticonvulsant treatment from having a child or changing a satisfactory drug regimen when the epilepsy is well controlled. Doctors should explain to parents that the increased risk is small and that many of the complications are minor or remediable.....Until further facts about the teratogenic risks of antiepileptic drugs are known, their various other side effects also need to be considered, and on balance carbamazepine or sodium valproate seems preferable to phenytoin or phenobarbitone as the first choice for the treatment of appropriate types of epilepsy in young girls and women in their reproductive years”.</i><sup>2</sup></p>
1982	<p>The data sheets for Epilim included the limitation on use by women of child-bearing age and the warning regarding the potential implications of the results of the tests conducted in animals, agreed with the licensing authority in 1974. These reflected the teratogenic effects of sodium valproate seen in animal studies:</p> <p><b>“Uses</b></p> <p><i>In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, Epilim should be used only in severe cases or those resistant to other treatment.”</i></p> <p><b>“Contra-indications, warnings, etc...</b></p> <p><i>Women of child-bearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have 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.”</i></p>
October 1982	<p>Sanofi received a copy of a report from investigators in the Rhone Alps region of France relating to cases of neural tube defect in infants born to mothers with epilepsy, who were reported as having been prescribed sodium valproate during pregnancy<sup>3</sup>. The flaws in the study, were noted by various commentators: the design was retrospective; it considered only children with congenital abnormalities and did not consider these in the context of all exposed infants; the confidence intervals were wide as a result of the small size of the study and the few cases of spina bifida observed, raising a possibility that the true results could be very different from those reported; and, of the nine cases of spina bifida reported in the study, two had a family history of the condition and were</p>

<sup>2</sup> Anonymous. Teratogenic risks of antiepileptic drugs. BMJ, 1981; 283: 515-516.

<sup>3</sup> Bjerkedal T., Czeizel A., Goujard J., Kallen B., Mastroiacova P., Nevin N., Oakley G., Robert E. Valproic acid and spina bifida. Lancet, 1982; ii:1096

	<p>therefore at high risk, irrespective of exposure to anti-epileptic medication during pregnancy). Nevertheless Sanofi considered the data seriously.</p> <p>Sanofi sent a copy of the report to the DHSS on 13 October 1982.</p>
December 1982	<p>The DHSS indicated to Sanofi that they did not believe the data available at that time were sufficient to establish a causal connection between use of sodium valproate and neural tube defects or that any change to the data sheet for Epilim was necessary, save for the inclusion of advice to doctors that pregnancies in women prescribed sodium valproate should be carefully monitored.</p>
1983	<p>During early 1983, Sanofi discussed the Rhone Alps data with a number of other experts. Their advice was that any well designed study attempting to reproduce the results obtained by Dr Robert would be impracticable, in view of the large numbers of patients it would be necessary to recruit, the small numbers of pregnant women who were prescribed Epilim, given the restriction on use of the product in women of child-bearing age and the associated warnings set out in the datasheet and the fact that any study would require participation by very substantial numbers of healthcare professionals.</p>
January 1983	<p>Following discussions with the DHSS, the datasheets for Epilim formulations were amended to add advice to prescribers that the use of sodium valproate, like certain other anti-convulsants, <i>“should be carefully monitored”</i> during pregnancy.</p>
	<p>The CSM’s <i>“Current Problems”</i> publication (a leaflet produced several times each year, intended to draw attention to matters of concern or interest which had been considered by the CSM and sent to all practising medical practitioners in the UK) included an article regarding the increased incidence of congenital malformations in children born to women with epilepsy prescribed sodium valproate and other anti-epileptic drugs. In particular, it referred to the difficulties interpreting reports of congenital abnormalities in infants born to mothers prescribed anti-epileptic treatment during pregnancy, in circumstances where <i>“it is difficult to determine whether it is the disease itself or the medication used in its treatment which is responsible for the increased malformation rate.”</i> Current Problems stated that, despite the apparent risk of malformations in children born to mothers with epilepsy prescribed anti-epileptic drugs, withdrawal of treatment <i>“is not generally advisable because foetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves.”</i> The recent data regarding the potential risks of neural tube defects, were referenced and the CSM concluded <i>“there is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other”</i>.</p>
April 1983	<p>An international symposium on epilepsy and sodium valproate was held. The President of the symposium was Professor Peter Jeavons of Aston University and the symposium was attended by over 200 experts in the field of epilepsy from the UK and Ireland and over 150 experts in the field of epilepsy from 14 other countries. This international symposium was supported by Sanofi.</p>

	<p>The report of the symposium, which was published as a supplement to the British Journal of Clinical Practice<sup>4</sup>, presents the papers given by various eminent epilepsy specialists at the symposium and records some of the discussions that took place.</p> <p>One of the papers, entitled “Teratogenicity of Anti-epileptic Drugs” was given by Dr Meinardi and Professor Lindhout from the Netherlands. These specialists expressed concern regarding the potential risk of congenital malformations in children exposed to phenytoin (another antiepileptic drug) during pregnancy and the debate among specialists in this area. They referred to the views of Professor Janz from Germany, who noted that, while children from pregnancies where the mother had received treatment with anti-epileptic medication had <i>“malformations about 1.5 times more often than children from untreated pregnancies”</i>, the findings did <i>“not indicate whether or not the difference [was] due to medication only”</i>, in circumstances where <i>“cases of epilepsy which require treatment and those which do not also differ with respect to other factors that may influence the occurrence of malformations”</i>. Professor Janz’s observation that <i>“the fact that malformations are only slightly less often observed in children of epileptic fathers than in children of epileptic mothers and that there is a tendency for malformations to recur in families”</i> was also mentioned as arguing <i>“against the teratogenicity of the anti-epileptic drugs”</i>. Dr Meinardi and Professor Lindhout concluded that it remained uncertain whether anti-epileptic drugs could be safely administered during pregnancy and stated <i>“the complexity of the question and the frequency of the event suggest an idiosyncrasy or a multifactorial cause. To unravel this problem, studies of such size are needed that only through international cooperation can sufficient information be collected. However, an international study will introduce many new variables which will be difficult or impossible to control.”</i></p> <p>The symposium was intended to promote debate between experts in relation to the benefits and risks of epilepsy treatments, including valproate. While therefore the symposium supplement in the British Journal of Clinical Practice was not peer reviewed and the papers presented reflected only the personal opinions of the speakers, the overall conclusion of the epilepsy experts who attended was consistent with the CSM’s Current Problems issued earlier in the year, that it was uncertain whether anti-epileptic medication, including sodium valproate, produced teratogenic effects in humans in view of the possibility that the effects which had been described, could be attributed to other factors, including epilepsy itself.</p>
25 May 1983	A product licence was granted for Epilim Uncoated Tablets 100mg (later changed to Epilim Crushable).
5 July 1983	A product licence was granted for Epilim Liquid, a sugar free formulation intended to be used as an alternative to Epilim Syrup.
February 1984	A bulletin issued by the World Health Organisation (“WHO”), “Drug Information January - December 1983”, included a section entitled “Valproate and Pregnancy”, which considered the implications of the Rhône-Alps data and also noted the potential biases arising from that study. In circumstances where the association reported in the Rhône-

<sup>4</sup> Third International Symposium on Sodium Valproate: proceedings of a symposium held at the Beau Sejour Conference Centre, St. Peter Port, Guernsey, Channel Islands, April 1983; Ed P.M. Jeavons; British Journal of Clinical Practice 1983; Symposium supplement 27.

	Alps analysis had either not been confirmed or had been rejected by other surveys undertaken in France, Italy and in South America, the bulletin concluded that the Rhône-Alps data did not identify sodium valproate as a more potent teratogen than other anti-epileptic drugs and noted that <i>“no Regulatory Authority has consequently reacted to restrict the use of valproate during pregnancy when it is likely to be effective and when a measure of seizure control is considered necessary”</i> (consistent with the indications section of the Epilim data sheet).
April 1985	<p>A paper published by DiLiberti in the American Journal of Medical Genetics<sup>5</sup> was drawn to the attention of the regulatory authority. The paper described seven children who had been exposed to sodium valproate in utero (mono and poly-therapy), who were said to have similar facial appearance; four had other congenital abnormalities and three had delayed psychomotor development.</p> <p>It was significant that a letter to the editor of the journal<sup>6</sup>, in response to DiLiberti’s paper, noted the confounding effect of poly-therapy and expressed the view that the 7 reported cases did not, in fact, have the same facial appearance. The fact that 3 of the children described by DiLiberti (although his conclusion refers to only 2 cases) seemingly had developmental delay was entirely consistent with the fact that these cases revealed confounding factors such as seizures during pregnancy, prematurity, low weight at birth and there was known to be an increased incidence of developmental problems in children born to mothers with epilepsy, both treated and untreated. While Sanofi considered the results of the study, the data, comprising a small number of selected cases, did not appear to be robust.</p>
1985	The third edition of the Textbook of Adverse Drug Reactions <sup>7</sup> stated that <i>“a variety of congenital defects have been described in infants exposed to sodium valproate in utero, including neural tube defects, cardiac abnormalities and oral cleft”</i> .
1986	<p>The 1985 CRM Annual Report included proposals, endorsed by the CSM, for the provision of information to doctors regarding use of medicines in pregnancy. These proposals were subsequently published as an Update in the BMJ in December 1986<sup>8</sup>. The CRM recommended that data sheets should include a statement about safety of the product when used in pregnancy and continued:</p> <p><i>“The Committee on Safety of Medicines and the Committee on Review of Medicines have recently considered data sheet pregnancy warnings. These should enable a doctor to make a balanced assessment between the potential risks to the foetus and the benefits to the mother and should comment on the following.</i></p> <p><i>Animal data: Any positive evidence of animal teratogenicity, embryotoxicity or other adverse effect on reproductive behaviour must be described and the</i></p>

<sup>5</sup> DiLiberti JH et al. The Foetal Valproate Syndrome. Am J Med Genet 1984; 19(3) 473

<sup>6</sup> Chessa L and Ianetti P. Fetal valproate syndrome. Am J Med Genet 1986; 24(2): 381-382

<sup>7</sup> The Textbook of Adverse Drug Reactions. Third Edition: Edited by DM Davies. Published Oxford University Press, 1985, P83

<sup>8</sup> CSM/CRM Update - Pregnancy warnings in data sheets. BMJ 1986; 293, 1495

	<p><i>nature of the abnormality or risk, the animal species, and the timing and dose relations specified.</i></p> <p><i>Human experience: Factual statements must be given on any human population studies and any anecdotal reports.</i></p> <p><i>Interpretation: While it is always appropriate to advise against the use of drugs in pregnancy unless there is an overriding clinical need, more specific advice should also be given, both for use of the drug in pregnancy and for use in women of child-bearing potential: (a) use is acceptable, (b) use in pregnancy only if the disease itself carries significant risks for the mother or child, (c) the drug is contraindicated in pregnancy.”</i></p> <p>The CRM additionally suggested specimen pregnancy warnings as guidance for the type and length of warnings that would be acceptable.</p>
May 1986	<p>Sanofi considered the results of further research carried out by Professor Lindhout and published in <i>The Lancet</i><sup>9</sup>. (Professor Lindhout had previously published research in 1984 in relation to the outcome of pregnancies exposed to valproate<sup>10</sup>). For the purposes of his 1986 paper he had contacted 13 centres in relation to the prevalence of neural tube defects in infants exposed to valproate in the first trimester and, by accumulating these data, he concluded that exposure to sodium valproate was associated with a risk of neural tube defect.</p> <p>There were discrepancies between the various papers published by Professor Lindhout in relation to the incidence of spina bifida in children exposed to valproate during pregnancy, which suggested that different methods had been used to collect cases and that pooling of potentially incompatible data had occurred.</p>
September 1986	<p>Following the conclusions of the 1985 CRM Annual Report, the Epilim data sheets were changed, to expand the existing information on use during pregnancy to reflect the data on animal teratogenicity and to include an entry summarising the potential risks in humans.</p>
1987	<p>The Oxford Textbook of Medicine Second Edition<sup>11</sup> stated that “<i>sodium valproate is a potent teratogen in animals and has been linked with congenital abnormalities (mainly neural tube defects) in humans</i>” (section 11.54)</p>
August 1987	<p>Sanofi submitted data to the CRM to support the review of the Product Licences for Epilim Plain Tablets (which were manufactured solely for export at that time), and Epilim Syrup, as requested by the DHSS. (While, at that time, Sanofi marketed other formulations of Epilim, these had all been licensed after 1976 and were not, therefore, subject to the CRM’s review.)</p>

<sup>9</sup> Lindhout and Schmidt. In-utero exposure to valproate and neural tube defects. *Lancet* I 1986; 14 June: 1392

<sup>10</sup> Lindhout and Meinardi, Spina Bifida and in-utero exposure to valproate. *Lancet* II 1984; 18 August: 396

<sup>11</sup> Oxford Textbook of Medicine. Second Edition. Editor DJ Weatherall. Published by Oxford University Press (1987)

November 1987	A paper by Professor Robin Winter and colleagues, entitled ‘Fetal Valproate Syndrome: Is there a recognisable phenotype?’ <sup>12</sup> was published in the Journal of Medical Genetics. This described four children who had been exposed to sodium valproate or valproic acid during pregnancy and suggested that they shared a common facial appearance. A range of other abnormalities were also reported, including hypospadias, cleft palate, and digital anomalies. A copy of the paper was forwarded to the DHSS by Sanofi. Two of the cases referenced in the paper were reported formally to the regulatory authority (one had already been reported by a doctor); the other two cases had previously been reported by Sanofi.
May 1988	Epilim Intravenous was licenced as a service to patients, for use in emergency situations, where a patient established on oral sodium valproate temporarily required intravenous therapy. The risk-benefit assessment associated with such usage was obviously very different from that associated with long term oral therapy and the application for the licence for the intravenous formulation was considered by the licensing authority on a stand-alone basis. Therefore, in contrast to the licence for oral formulations of Epilim, at the direction of the CSM, the indications section of the licence did not include a restriction regarding use of the product in women only in severe cases or those resistant to other treatment. However, the licence did include an expanded pregnancy warning reflecting scientific knowledge at the time of the application and referring to the available data regarding the potential teratogenic effects of sodium valproate in humans, consistent with Sanofi’s review following consideration of the CRM’s proposals. As a result of the particular circumstances in which Epilim Intravenous would be used and the differences from long term oral therapy, Sanofi continued to consider the data sheet wording for this formulation separately from that for oral formulations of Epilim, although sought consistency where this was appropriate.
June 1988	<p>Sanofi applied to the DHSS, under standard procedures, outside the CRM, to vary the pregnancy warning for the oral formulations of Epilim to bring them into line with the data sheet for Epilim Intravenous and to include a specific warning regarding the potential risk of “congenital abnormalities” (which would include spina bifida) in infants exposed to sodium valproate during pregnancy.</p> <p>However, the DHSS, refused to approve the variations for the oral formulations without full consideration by the CSM, because Epilim Intravenous had been assessed as a stand-alone product for short-term use in circumstances where the risk-benefit profile was likely to be different from that associated with other Epilim formulations.</p>
August 1988	The DHSS Medical Advisor to the CRM requested Sanofi to include a pregnancy warning in the data sheets for Epilim Plain Tablets, and Epilim Syrup (the only Epilim formulations being considered by the CRM) similar to that present in the data sheet for Epilim Intravenous, in order to reflect the available scientific data and to give consistency for all Epilim formulations. Sanofi welcomed this proposal which reflected the application made by the company in June, under standard procedures, for all oral formulations of Epilim.
	Sanofi wrote to the Senior Medical Officer at DHSS, who was involved with the Epilim Intravenous product licence and who would also deal with any application to vary the

<sup>12</sup> Winter et al. Foetal Valproate Syndrome: Is there a recognisable phenotype? J Med Genet 1987; 24: 692

	<p>licences of the oral Epilim formulations that were not subject to the CRM review, so that she was aware of the changes to the data sheets for Epilim Plain Tablets and Epilim Syrup proposed by the CRM and to request approval for similar changes to the oral Epilim formulations which were not subject to the CRM review.</p>
September 1988	<p>The British National Formulary Number 16 included the following statements:</p> <p>Chapter: Prescribing in pregnancy (page 31)</p> <ul style="list-style-type: none"> <li>• Table of drugs to be avoided or used with caution in pregnancy</li> </ul> <p>Valproate: Increased risk of neural tube defects reported; neonatal bleeding and hepatotoxicity also reported</p> <p>Chapter Anti-epileptics – Sodium Valproate</p> <ul style="list-style-type: none"> <li>• Sodium Valproate (page 183): <ul style="list-style-type: none"> <li>o Cautions: pregnancy and breast-feeding (see notes above)</li> </ul> </li> </ul> <p>The British National Formulary is published jointly by the British Medical Association and the Royal Pharmaceutical Society (previously the Royal Pharmaceutical Society of Great Britain) based on evaluations of clinical evidence from diverse sources with information validated by a network of clinical experts. Its content is authoritative and it is widely used as a reference by healthcare professionals.</p>
3 October 1988	<p>Sanofi received a letter from Dr Keen of the Association for Spina Bifida and Hydrocephalus (“ASBAH”), which expressed concern at the reported association between use of sodium valproate in pregnancy and spina bifida in exposed infants and suggested that the data sheet for Epilim could be modified to provide a clearer warning. Sanofi met with Dr Keen, a paediatrician, shortly afterwards. Sanofi had recently carried out an update to its review of Epilim in Pregnancy and, while the DHSS had recently reviewed the data sheet for Epilim and believed the warnings to be acceptable, Sanofi was considering a change to the data sheet to include specific reference to the questions raised about a potential association with spina bifida. Sanofi advised Dr Keen that any change would be subject to regulatory approval and that there could be some delay, particularly in circumstances where Epilim was undergoing review by the CRM.</p> <p>Sanofi was, at that time, preparing the first patient information leaflet (PIL) for Epilim and took the opportunity to canvass Dr Keen’s views on the type of information that could usefully be provided by Sanofi to patients in relation to this type of product. His opinion, which was typical of clinicians generally at that time, was that a PIL should encourage patients to discuss their medical condition and treatment with their own doctor. In particular, he expressed the view that information could more appropriately be conveyed from person to person (i.e. between doctor and patient) rather than in a generic leaflet, which could not reflect the particular circumstances of the individual patient.</p>
Late 1988	<p>After considering emerging data regarding the incidence of spina bifida and in view of the desirability of achieving harmonisation across different territories with respect to the information provided to doctors, Sanofi commenced preparation of applications to vary the product licences for oral Epilim formulations. In general, Sanofi adopted a cautious approach to the wording of its data sheets and sought to provide information and warnings to doctors as soon as the evidence raised a reasonable suspicion of an</p>

	<p>association with an adverse effect, even if this was far from demonstrating a causal relationship. Accordingly, the revised data sheet wording proposed by Sanofi included not only a specific reference to spina bifida, taking into account the views of the Association for Spina Bifida and Hydrocephalus and their strong belief that a reference in the data sheets for Epilim to a potential risk of neural tube defects in babies exposed to sodium valproate during pregnancy, would alert doctors to the need for antenatal screening, but also a recommendation in relation to use of valproate monotherapy, where the product was used during pregnancy, in order to achieve consistency with data sheets in other territories and to reflect the emerging scientific data suggesting an increased risk of congenital abnormalities in infants exposed to polytherapy regimes of anti-epileptic medication generally. It also instructed doctors that patients should be informed of the possible risks associated with use of the valproate during pregnancy.</p>
January 1989	<p>Sanofi received a letter from the Principal Medical Officer to the CSM requesting that the pregnancy statement in the Epilim data sheets should be expanded to include a statement on neural tube defects, their possible incidence, and recommendation regarding screening of pregnant women on valproate. At this stage, the CRM's amendments following the review of the product licences for Epilim Plain Tablets and Epilim Syrup (including the revisions to the pregnancy section of the data sheet) had been approved by the medical assessor but the full review by the CRM had not been completed and had not therefore been taken into account by Principal Medical Officer. Furthermore, as indicated above, Sanofi had been conducting a review of the product information and was, at that time, in the process of preparing an application to vary the information in the data sheet including a reference to neural tube defects.</p>
16 January 1989	<p>Applications for variations to the product licences for Epilim formulations were submitted to the DHSS.</p>
	<p>The DHSS Principal Medical Officer considered the proposed amendments to the pregnancy warning for Epilim data sheets and approved these, subject to reiterating her view that the potential incidence of neural tube defects in infants exposed to sodium valproate in utero should be provided. Sanofi agreed with DHSS that the Epilim data sheets would include an estimated incidence of 1%, while recognising that the available evidence was limited to relatively small numbers of patients and was subject to biases and confounding, such that it was difficult to provide reliable information regarding the incidence of these abnormalities.</p>
April 1989	<p>The applications to amend the data sheets for Epilim were approved by the regulatory authority to incorporate the following wording:</p> <p><i>“Women of child-bearing age.</i></p> <p><i>An increased incidence of congenital abnormalities in off-spring born to mothers with epilepsy both untreated and treated has been demonstrated.</i></p> <p><i>There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.</i></p>

	<p><i>In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and the patients should be informed of these and the need for screening”.</i></p> <p>At the request of the regulatory authority, Sanofi sent copies of the revised data sheet to all GPs and relevant hospital doctors, with a covering letter which said <i>“The datasheet has always drawn attention to the use of Epilim in women of child bearing age and the need for monitoring. This has now been extended to provide more specific and practical advice based on appropriate ante-natal screening and informed counselling”.</i></p>
	<p>An international symposium was held. This symposium was again attended by over 200 experts in the field of epilepsy from the UK and Ireland and approximately 200 experts in the field of epilepsy from 13 other countries. This international symposium was supported by Sanofi. It was comprised of papers given by eminent experts in epilepsy subsequently published by the Royal Society of Medicine<sup>13</sup>. The symposium included a session entitled <i>“Management of the Pregnant Patient with Epilepsy”</i>, which provided perspectives from an obstetrician and a neurologist: the obstetrician, Dr Robertson emphasised the potential risk to the foetus as a result of seizures in the pregnant mother; the neurologist, Professor Loiseau from Bordeaux commented on the risk of major malformations, minor anomalies and developmental disturbances in children born to mothers with epilepsy, stating that the risk of such matters was multifactorial <i>“with genetic, environmental and therapeutic components”</i>. Professor Loiseau said that <i>“as all epileptic drugs are weak teratogenic agents, it is not necessary to change a beneficial therapy and indeed most epileptic women are reluctant to change their medication”</i>, although he referred to the desirability of monitoring all such pregnancies, including those where sodium valproate was used, for the presence of neural tube defects.</p> <p>Like the previous symposium in 1983, this symposium was intended to promote debate between experts in relation to the benefits and risks of epilepsy treatments, including valproate notably during pregnancy. Again, the publication of the proceedings, this time in the Royal Society of Medicine; International Congress and Symposium Series, was not peer reviewed and the papers presented reflected only the personal opinions of the speakers.</p>
<p>May 1989</p>	<p>The BMJ published an article by Oakeshott and Hunt<sup>14</sup> which referred to the risk of congenital abnormalities associated with maternal epilepsy and its treatment. The paper highlighted the importance of screening pregnant women taking sodium valproate for the presence of spina bifida in the foetus. The article was concerning in that it reported three cases of spina bifida in children born to women taking sodium valproate between 1983/4 and 1986, who had either not been screened at all or who had undergone screening late in pregnancy when therapeutic abortion could not be considered. By the time this article was published, the data sheet had already been revised to include information in relation to the potential risk of neural tube defects</p>

<sup>13</sup> Fourth International Symposium on sodium valproate and epilepsy: proceedings of a symposium held in St Helier, Jersey, Channel Islands, April 1989; Ed D Chadwick; Royal Society of Medicine; International Congress and Symposium Series 152

<sup>14</sup> Oakeshott P and Hunt GM. Lesson of the Week: Valproate and spina bifida. BMJ 1989; 298: 1300

	and a decision had been made to send copies of the revised data sheet to individual doctors.
16 August 1989	<p>The first PILs for Epilim (Epilim EC, Epilim Crushable, Epilim Syrup and Epilim Liquid) received approval from the DHSS.</p> <p>The PIL closely followed the format recommended in the Guidelines prepared by the Association of the British Pharmaceutical Industry (ABPI) and precedent leaflet (as described in the response to Q14). It advised patients to read the leaflet before commencing treatment with Epilim, stating: <i>“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”</i>. In addition to this overarching statement, the PIL contained three separate statements regarding pregnancy, aimed at women of child-bearing age, reflecting Sanofi’s wish to ensure that any patient who continued to take Epilim during pregnancy only did so after proper discussion with their treating doctor about the potential risks and benefits of such treatment in the context of their particular medical condition and circumstances.</p> <p>The first statement, which was highlighted by being contained in a large bordered box under the heading <i>“Things to remember about Epilim”</i>, advised patients: <i>“If you are likely to become pregnant, tell your doctor”</i>.</p> <p>In addition, the leaflet included a separate section headed <i>“Before taking your medicine”</i> which set out a number of questions under the following sentence: <i>“If you can answer YES to any of the following questions tell your doctor. He may need to give you special instructions”</i>. The question aimed at women of child-bearing age stated: <i>“Are you pregnant or likely to become pregnant?”</i></p> <p>Finally, the following statement was set out towards the end of the PIL: <i>“Epilim may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly”</i>.</p> <p>The PIL concluded, consistent with the ABPI guideline, that the: <i>“leaflet provides a summary of the information available on your medicine”</i> and emphasised again <i>“for further information consult your doctor or pharmacist”</i>.</p>
1990	The CRM review for Epilim Plain Tablets was completed.
1990	The report of a study conducted between 1982-1988 to investigate the effects of anti-epileptic drugs during pregnancy was published <sup>15</sup> . Sanofi had been contacted by the investigators and had provided financial support for the study. The study followed women with epilepsy during their pregnancies and collected information regarding age, social class, anti-epileptic medication and other treatment, the occurrence of seizures and complications during pregnancy. All the babies were examined for the presence of congenital abnormalities immediately after delivery. The study recruited 88 women

<sup>15</sup> Hunter R and Allen E, The course and outcome of pregnancy in women with epilepsy - a 6-year prospective study, J.Obstet.Gynaecol., 1990, 10(6), 483-491

	<p>with epilepsy (95 pregnancies resulting in 92 babies); 25 of the pregnancies were exposed to sodium valproate. Some of the cases were also incorporated in a paper by Lindhout et al<sup>16</sup>.</p> <p>Overall, the incidence of major congenital malformations was 1.1 per 100 live births and, for minor congenital malformations, was 8.7 per 100 live births. The single major congenital malformation recorded during the study was a case of spina bifida in a baby exposed to sodium valproate. However, the investigators concluded that exposure to sodium valproate could not have been implicated in that case; the mother did not commence treatment until she was 20 weeks pregnant, at which stage organogenesis would have been complete. There were eight minor malformations identified in the study, which included two cases of talipes (clubfoot) and one case of polydactyly (an additional digit) in children exposed to sodium valproate monotherapy and one case of talipes in a child exposed to sodium valproate and carbamazepine. The investigators concluded: <i>“Our results show that neonatal outcome in our epileptic women also compared favourably with the neonates born to control women, who are matched for age, parity and social class. We could not demonstrate any effect of epilepsy on birth weight or head circumference or between babies exposed to different anti-convulsant drugs in utero”</i>. They suggested that the high incidence of minor congenital abnormalities might be associated with folate deficiency.</p>
September 1990	The CRM granted a renewed licence for Epilim Plain Tablets.
January 1991	The CRM granted a renewed licence for Epilim Syrup.
September 1991	Based on regular surveillance practice, Sanofi applied to vary the product licences for Epilim products to make further changes to the data sheet.
October 1991	<p>The regulatory authority (which had recently become the Medicines Control Agency (“MCA”)) approved the proposed wording in the Epilim datasheet:</p> <p><i>“Women of child-bearing age.</i></p> <p><i>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.</i></p> <p><i>The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.</i></p> <p><i>In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against</i></p>

<sup>16</sup> Lindhout and Schmidt, In-utero exposure to valproate and neural tube defects. Lancet (1986) 1392

	<i>the possible risks and patients should be informed of these and the need for screening.”</i>
November 1991	The licensing authority granted a product licence for Epilim CR 300mg, a controlled release formulation of sodium valproate intended to provide smoother serum levels, without the same peaks and troughs associated with previous formulations.
20 January 1992	A PIL for Epilim CR 300 incorporating the same wording as that for other oral formulations of Epilim, was approved by the MCA.
April 1992	<p>Sanofi considered the views of epilepsy specialists, as reflected in consensus guidelines, such as the influential guidelines on preconception counselling, management and care of the pregnant women with epilepsy, issued by Delgado-Escueta and Janz in 1992<sup>17</sup>. These guidelines assessed the available information regarding various anti-epileptic drugs (AEDs) and concluded that:</p> <p><i>“...each of the four major AEDs [Phenytoin, Carbamazepine, Valproate and Phenobarbitone] has been considered more teratogenic than the other three AEDs, depending on the author cited, but that results are confounded by the use of polypharmacy, different dosages and combinations of AEDs, different patient populations and different genotypes exposed to the AEDs. ... Since no agreement has been reached regarding which AED is the most teratogenic, the present consensus opinion is that the AED that stops seizures in a given patients should be used. Often, this is the drug of choice for a given seizure type and epilepsy syndrome.”</i></p> <p>The authors considered the issue of developmental delay in children exposed to AEDs in pregnancy and concluded that the available evidence indicated that any increased risk <i>“was not associated with exposure to AEDs but with seizures during pregnancy, specifically with partial seizures in mothers and with low paternal education”</i>. The guidelines recommended that in pregnancy, the first choice drug for seizure type and epilepsy syndrome should be prescribed, as monotherapy at the lowest dose and plasma level that protects against tonic-clonic seizures as it was recommended in the data sheet.</p>
1993	<p>The name of the Epilim CR 300mg formulation was changed to Epilim Chrono Controlled Release, consistent with the name used in other territories.</p> <p>200mg and 500mg dosage forms of Epilim Chrono were approved by the licensing authority.</p>
December 1993	<p>Following an application by Sanofi, the MCA approved the following amendment to the data sheets for Epilim:</p> <p><i>“Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence</i></p>

<sup>17</sup> Delgado-Escueta and Janz. Consensus Guidelines: Pre-conception Counselling, Management, and Care of the Pregnant Woman with Epilepsy. Neurology 1992; 42 (Suppl 5): 149

	<p><i>exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.</i></p> <p><i>The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate”.</i></p>
1994	<p>The product licence for Epilim Liquid was renewed and the format of the PIL was therefore revised in accordance with SI 1992/3294. The PILs for all other formulations of Epilim were updated voluntarily at the same time, ensuring consistency across the product range.</p>
August 1994	<p>The revised PILs were approved and included the following wording:</p> <p><i>“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 sodium valproate during pregnancy to control their epilepsy have about a 1% chance of having a baby with spina bifida. This however can usually be detected in the first part of pregnancy by normally used screening tests. Taking dietary supplements of folate may lower the risk of having a baby with spina bifida. It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor <u>as soon as you know</u> you are pregnant”.</i></p>
Late 1994	<p>At the end of 1994, Professor Lindhout gave a lecture at the Walton Centre in Liverpool on the subject of epilepsy in pregnancy. The subject matter was of particular interest to Sanofi and the lecture was therefore attended by a representative from the company, who prepared a written note of the content.</p> <p>The note indicates that Professor Lindhout commented on the difficulties carrying out research in this area. Major congenital malformations occur at low frequency, so it is therefore necessary to recruit a large number of patients in order to detect any change in the frequency of such events. In the context of epilepsy, there are many genetic factors related to the type of epilepsy which may influence the occurrence of congenital abnormalities. It is therefore problematic to identify an appropriate control population for any study. Furthermore, when considering issues related to the development of the child, it was difficult to separate out the potential effect of a mother with severe epilepsy influencing a child’s development, from the effects of antenatal exposure.</p> <p>The note states that Professor Lindhout referred to new data suggesting a dose effect between sodium valproate and the incidence of spina bifida. In particular he suggested that peak plasma concentrations appeared to be significant as well as total daily dose and monotherapy. Professor Chadwick, who was present at the meeting, asked whether there should be a move to switch more difficult cases on higher doses of sodium valproate to other therapies. Professor Lindhout’s view was that, if a therapeutic alternative was available, then it would be reasonable to switch those on</p>

	<p>high doses to an alternative treatment, but that for some patients there would be no alternative to sodium valproate.</p> <p>The lecture by Professor Lindhout was not subsequently published and the account set out above is therefore based solely on the contemporaneous note prepared by the Sanofi attendee. The content was not, of course, peer reviewed.</p>
September 1995	<p>A review article, which referred to so-called “Foetal Valproate Syndrome”, under the heading “Syndrome of the Month”, was published by a group from Manchester in the Journal of Medical Genetics<sup>18</sup>. The authors were Dr Jill Clayton-Smith and Professor Donnai (who had also been an author of an earlier paper in 1987). Sanofi became aware of the paper shortly after publication and it was reported to the MCA. It referred to the increased incidence of major and minor congenital abnormalities in infants born to epileptic mothers and listed the factors which might contribute to such an increase, including the occurrence of seizures, an inherited predisposition to malformations and the teratogenic effects of anti-epileptic medication. The authors referred to congenital abnormalities described in children exposed to sodium valproate including facial anomalies and congenital malformations (neural tube defects, congenital heart disease, cleft lip and palate, genitourinary malformations, tracheomalacia, radial ray defects, arachnodactyly, overlapping digits and abdominal wall defects). The information provided to doctors in the data sheet for Epilim at that time, provided explicit information regarding the risks of neural tube defects, multiple malformations and facial dysmorphism, which were the focus of this paper.</p>
March 1996	<p>Sanofi applied to the MCA to amend the data sheet to expand the warnings in relation to use of Epilim in pregnancy. The proposed changes comprised insertion of the words that associated congenital abnormalities were “<i>particularly of the limbs</i>” and an amendment of the risk of neural tube defects to “<i>1 to 2%</i>”. In circumstances where Epilim Chrono had recently been authorised for administration in a once daily regime, the amendment to the data sheets also advised doctors that they should prescribe the lowest effective dose “<i>in divided doses</i>”.</p>
9 May 1996	<p>These changes were approved by the MCA.</p>
14 June 1996	<p>Further changes to the PILs for Epilim were approved. The revised PIL amended the second sentence of the pregnancy warning as follows:</p> <p style="text-align: center;"><i>“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.”</i></p>
September 1997	<p>A study by Samren and colleagues was published in 1997<sup>19</sup>. This study posted data from 5 prospective studies involving 1,379 children in total and considered the incidence of major congenital abnormalities. The authors found an increased incidence of major congenital abnormalities in children exposed to sodium valproate or to carbamazepine</p>

<sup>18</sup> Clayton Smith J and Donnai D. Foetal Valproate Syndrome. J. Med Genet. 1995; 32:724

<sup>19</sup> Samrén EB et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia. 1997 Sep; 38(9):981-90.

	<p>compared with non-epileptic controls. The data also suggested that major congenital malformations occurred more frequently in children exposed to higher doses of sodium valproate during pregnancy.</p> <p>The data sheet for Epilim informed doctors of the potential risks of congenital abnormalities associated with sodium valproate and advised that, in pregnancy, the lowest effective dose should be used. It was therefore consistent with this emerging information.</p>
June 1997	<p>Dr Peter Turnpenny, a clinical geneticist from Exeter, gave a presentation regarding the existence of “foetal valproate syndrome”. Sanofi, wrote to him to request details of the four children he had described, who apparently displayed facial dysmorphism and social behavioural problems. Sanofi sent forms to Dr Turnpenny for him to report these cases to Sanofi and went to visit him in Exeter to discuss the evidence he relied upon in relation to the existence of the syndrome. Dr Turnpenny subsequently suggested that Sanofi might provide financial support for a scientific conference on epilepsy in pregnancy that he was considering setting up at that time. Sanofi provided a grant for a forum at which the evidence relating to the effects of anti-epileptic drugs on the foetus could be discussed by specialists in the field, which was ultimately held in May 1999</p>
23 June 1997	<p>Based on the new International Conference on Harmonisation (ICH) standard, a Periodic Safety Update Report (PSUR) in relation to Epilim formulations, which covered the period February 1992 to January 1997, was submitted to the UK regulatory authority. PSURs are pharmacovigilance documents intended to provide safety updates resulting in an evaluation of the impact of the reports on the risk-benefit balance of a medicinal product, taking into account new or emerging safety information (including in relation to use in pregnancy). The MAH is required to submit a PSUR at defined time points post-authorisation.</p> <p>The report, which included all events reported worldwide, concluded that there was “no suspicion of increased frequency or severity of already listed reactions over this period”, that “no new and relevant information about use in pregnancy was identified during the review period” but stated “appropriate monitoring with regard to pregnancy during this period is recommended”. The PSUR expressed the view that the current data sheet appropriately reflected the available evidence for sodium valproate.</p>
19 September 1997	<p>The MCA approved a further variation to the Epilim data sheets, to include a warning in respect of the risk of haemorrhagic syndrome in new-born infants whose mothers had taken sodium valproate during pregnancy: “<i>there may also be blood clotting problems in the new born if the mother has taken Epilim during pregnancy</i>”.</p> <p>Shortly afterwards, the data sheets for Epilim were replaced by Summaries of Product Characteristics (SmPCs), the contents of which were defined by Directive 83/570/EEC and are now set out in Article 11 of Directive 2001/83/EC (see response to Q14)</p>
September 1999	<p>Sanofi provided financial support of £15,000 to Professor Chadwick’s group in Liverpool for their study investigating additional educational needs in children born to mothers with epilepsy.</p>

<p>18 January 2000</p>	<p>The MCA wrote to Sanofi, indicating that they were <i>“investigating a potential drug safety signal of an increased odds of developmental delay in children of mothers exposed to valproate in utero compared to other antiepileptic drugs”</i>. They requested Sanofi’s comments and that all other relevant information be submitted to them, and set up a meeting to discuss the issue.</p>
	<p>Sanofi contacted the MCA to request further details in relation to the letter and was told that this had been prompted by their receipt of a draft paper by Professor Chadwick <i>“Additional Educational Needs in Children Born to Mothers with Epilepsy”</i> arising from a study supported financially by Sanofi. The study reported on the results of a retrospective postal questionnaire sent to women aged between 16 and 40 registered at the Mersey Regional Epilepsy Clinic and examined the association between additional educational needs (“AEN”) as measured by whether the child attended a mainstream or special school, required additional help, or had received a statement of additional educational need) and exposure to AEDs. It found that compared to unexposed children, the odds ratio for AEN in children exposed to sodium valproate monotherapy was 3.4 (95% CI 1.63-7.10). When the figures were adjusted to include only first born children (to explore the possible bias introduced by the inclusion of siblings) the odds ratio was 1.89 (95% CI 0.64-5.61). Polytherapy including valproate had similarly high odds ratios for AENs compared with those unexposed of 2.51 ( 95% CI 1.04–6.07) versus the odds ratio of 1.51 ( 95% CI 0.56–4.07) for polytherapy excluding valproate</p> <p>The conclusion of the study was: <i>“Although the findings should be treated with caution, they suggest that monotherapy or polytherapy with valproate during pregnancy carries particular risks for the development of children exposed in utero”</i>.</p>
<p>10 February 2000</p>	<p>Sanofi corresponded with Professor Chadwick who recognised that his retrospective study was a preliminary step that required further investigation. Professor Chadwick explained that he had submitted two papers for publication. One was a meta-analysis of sodium valproate compared to carbamazepine and the other was the retrospective study reviewing educational needs in children born to mother with epilepsy. Both had been rejected by The Lancet, but had subsequently been submitted to the BMJ. Professor Chadwick indicated that he knew the retrospective study had statistical flaws, and said that he had asked the MCA’s statistician to review it. The MCA statistician queried whether the association between developmental delay and sodium valproate was an a priori hypothesis of the study, or whether it was a data dependent finding. He raised various other questions including the extent to which the age of the children and mothers, the type of epilepsy suffered by the mothers, and familial factors had been considered.</p> <p>Sanofi was concerned to establish whether the data demonstrated emerging evidence of a genuine association, or whether they were a false signal reflecting the type of factors identified by the MCA statistician. Like him, Sanofi noted that a lot of information was missing due to the retrospective nature of the study (retrospective postal questionnaire with no medical assessment) that only a small number of children were identified as having AEN, the fact that many confounding factors were not taken into account (i.e. nature of the epilepsy, seizures during the pregnancy) and that only a prospective study with a long follow-up could properly address the issues; the company</p>

	<p>therefore decided to support the prospective study proposed by Dr Chadwick on neurodevelopmental effects of antiepileptic drugs.</p>
<p>3 April 2000</p>	<p>Sanofi asked external experts to analyse the Professor Chadwick’s study and submitted, based on the resulting assessment, a detailed response to the MCA. This reviewed all of the available data on AEDs and developmental delay including clinical and preclinical data, an analysis of reports from the Corporate safety database, and unpublished data, including Professor Chadwick’s study. It also reviewed possible causes of developmental delay (other than AED exposure) that could have confounded the results of the study including:</p> <ul style="list-style-type: none"> <li>• maternal epilepsy</li> <li>• seizures during pregnancy</li> <li>• the influence of complications during pregnancy and at birth</li> <li>• genetic factors; and</li> <li>• environmental factors, such as parental intelligence and social environment.</li> </ul> <p>The report concluded that:</p> <p><i>“A specific feature of the treatment of pregnant women with epilepsy is that the potential benefits of seizure control in the mother must be weighed against the potential risk of the antiepileptic to both the mother and the foetus.</i></p> <p><i>Children of mothers with epilepsy exposed to AEDs in utero, have been shown in some studies to have lower scores on a variety of cognitive development measurements when compared to controls. The differences suggest that they are at greater risk for academic difficulties than control children.</i></p> <p><i>Maternal epilepsy and type of epilepsy (generalised versus partial), intrauterine exposure to AEDs, hereditary factors, parental education, psychosocial and socio-economic status, and other confounding factors, may all play a role in increasing the risk of developmental delay in children born to mothers with epilepsy.</i></p> <p><i>As of today, from the data available, considering the complex interaction between epilepsy and environmental factors, there is no clear-cut evidence that any one of the major antiepileptic drugs has a higher risk than any other of causing developmental delay in children exposed in utero.</i></p> <p><i>In summary, the evidence to date does not suggest a formal or quantifiable relationship between AED use, including valproate, and developmental delay in children born to mothers treated during pregnancy.”</i></p> <p>Sanofi also pointed out that the SmPC in force for the product at that time already restricted the use of sodium valproate in women of childbearing age as follows: <i>“In women of childbearing age valproate should be used only in severe cases or in those resistant to other treatment.”</i> The risk/benefit analysis already dictated that the drug should only be used in pregnant women where their epilepsy could not be effectively controlled by using other drugs. As a result of this restriction it was likely that there</p>

	was a higher prevalence of severe epilepsy in the population of women of child bearing age treated with sodium valproate.
June 2000	The MCA requested further detail on preclinical studies relating to teratogenicity in rats that had been referenced by Sanofi in its initial response.
10 July 2000	Sanofi wrote to the MCA submitting the PSUR for sodium valproate for the period 1 February 1997 - 31 December 1999. This PSUR included a cumulative review on “psychomotor development impaired”. The conclusions were: <i>“From the data presented in this safety update, the cumulative experience to date and literature, a new area of interest has been identified namely development delay. Based on current information no definite relationship can be established between valproate and development delay in children exposed in utero to valproate. Nevertheless, this topic will remain under surveillance”</i> .
26 July 2000	Sanofi provided summaries of the requested preclinical studies to the MCA.
August 2000	Sanofi, and other pharmaceutical companies, provided financial support for Professor Chadwick’s prospective study of Standard And New Antiepileptic Drugs (“SANAD”). Professor Chadwick’s SANAD trial was a randomised clinical trial with patients randomised to sodium valproate and other antiepileptic drugs. The primary objective was to study whether there were differences in IQ between mothers and children exposed to AEDs in pregnancy. The SANAD study had already been underway for 12 months, and Sanofi agreed to support its continuation.
September 2000	The data on developmental delay were reviewed by the Pharmacovigilance Subcommittee of the CSM.
15 September 2000	Sanofi wrote to the MCA confirming that it was sponsoring two studies investigating developmental delay, being carried out by Professor Chadwick’s group in Liverpool. The letter stated that Sanofi would provide details and a summary of the methodology of these studies when these became available. The letter also indicated that Sanofi was providing support for two pregnancy registers, the European Registry of Antiepileptic drugs and Pregnancy (“EURAP”) and the UK Epilepsy and Pregnancy Register.
December 2000	Nine variation applications had already been submitted to the MCA, the purpose of which was to harmonise and update the various sodium valproate SmPCs in line with the company core safety information (“CSI”), as well as to add warnings relating to pancreatitis and weight gain. In line with EU guidance, the revised SmPC wording re-ordered some of the existing pregnancy warnings. It also included, at section 4.4, a new special warning concerning the use of Epilim in women of child-bearing age. The restriction on the use of Epilim to women with severe epilepsy or those resistant to other treatment was therefore moved from the indications to the special warnings section of the SmPC. The warning read:  <i>“Pregnancy: It is recommended that Epilim be used in women of child-bearing age only in severe cases or those resistant to other treatment because of the potential teratogenic risk to the foetus exposed to valproate in utero. Women of child-bearing age should be informed of the potential risks and benefits of</i>

	<i>continuing anti-epileptic treatment throughout pregnancy (see also Section 4.6 Pregnancy and Lactation)."</i>
January 2001	The MCA confirmed that the developmental delay data had been discussed extensively at the Pharmacovigilance and Paediatric Sub-Committees of the CSM, who considered that a causal association between developmental delay in infants and exposure to sodium valproate in utero had not been established and that no immediate regulatory action was therefore required.
	Professor Chadwick's retrospective study was subsequently published in the Journal of Neurology, Neurosurgery and Psychiatry <sup>20</sup> .
4 March 2001	The MCA wrote to Sanofi confirming the information provided in January and the CSM's conclusion that: <i>"...based on the presently available evidence, a causal association had not been established [between sodium valproate and developmental delay]"</i> . However, the authorities considered that treating physicians should have emphasised to them the existing restriction on the use of sodium valproate in women of childbearing age to those who were resistant to other treatments and those who suffered from severe epilepsy.  Sanofi contacted the MCA's assessor, who confirmed that the CSM's request had been addressed by Sanofi's earlier (December 2000) variation applications.
27 June 2001	Sanofi wrote to the MCA submitting the PSUR for sodium valproate for the period 1 January 2000 - 31 January 2001. This PSUR included a cumulative review on <i>"psychomotor development impaired"</i> , which concluded: <i>"Regarding developmental delay, based on data collected through spontaneous reporting, no conclusions concerning a causal relationship between valproate and occurrence of "developmental delay" in children born to mothers exposed to valproate in utero can be drawn. This topic will remain under close surveillance by the company"</i> . The reports of administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the CSI.
October 2001	The SmPC changes proposed by Sanofi in December 2000 were approved by the MCA.
21 December 2001	Sanofi wrote to the MCA submitting the PSUR for sodium valproate for the period 1 February 2001 to 31 July 2001. The reports of administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the CSI.
January 2002	Articles raising concerns about the potential teratogenic (congenital malformation) effects of valproate, including some that mentioned the data from the UK Epilepsy and Pregnancy Register, were reported in the general press. These publications related to congenital malformations which were already listed in the SmPC. Therefore, while Sanofi continued to be restricted in its ability to communicate directly with members

<sup>20</sup>Adab N, Jacoby A, Smith D, Chadwick D: Additional educational needs in children born to mothers with epilepsy: *J Neurol Neurosurg Psychiatry* 2001;70:15-21

	<p>of the public in relation to Epilim, by this time, information regarding the possible risks associated with use of valproate in pregnancy was being reported in the lay media.</p> <p>While Sanofi does not provide a comprehensive list of such press reports, examples appeared in The Times on 24, 25 and 28 January 2002.</p>
28 January 2002	<p>MCA notified Sanofi that the issue of potential neurodevelopmental delay in children exposed to valproate during pregnancy was being kept under constant review, but for the time being, and pending consideration of data from the UK Epilepsy and Pregnancy Register, no amendment to the warnings and advice contained in the product information for Epilim were required.</p>
8 May 2002	<p>Sanofi wrote to the MCA submitting the PSUR for sodium valproate for the period 1 August 2001 to 31 January 2002. This PSUR included a cumulative review on <i>“psychomotor development impaired”</i>. No conclusion was reached following the review and these adverse reactions therefore remained under surveillance by the company. The reports of administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the CSI.</p>
22 July 2002	<p>The MCA wrote to Sanofi stating that the CSM had carried out a further review of the safety of sodium valproate in pregnancy, in the context of preliminary data from the UK Epilepsy and Pregnancy Register. The CSM had advised that <i>“there was evidence to suggest that although all antiepileptic drugs were potentially teratogenic, there was an increased risk of teratogenicity with valproate compared with other antiepileptic drugs.”</i> In the light of this the CSM had advised the MCA to communicate with prescribers and health professionals about the potential teratogenic risks of sodium valproate and other AEDs.</p>
August 2002	<p>In order to take into consideration questions raised by recent reports in the scientific literature concerning the potential developmental delay reported in children born to mother with epilepsy, Sanofi modified its CSI in August 2002 as follows:</p> <p style="text-align: center;"><i>“PREGNANCY</i></p> <p style="text-align: center;"><i>- Risk associated with epilepsy and antiepileptics</i></p> <p style="text-align: center;">...</p> <p style="text-align: center;"><i>Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus“.</i></p>
12 September 2002	<p>Sanofi responded to the MCA’s letter of 22 July, in relation to the conclusions that could be drawn from the UK Epilepsy and Pregnancy Register data. The results showed that there was a statistically significant difference between carbamazepine and valproate monotherapy, but no difference between valproate and the other anti-epileptic drugs</p>

	<p>with regard to the risk of major congenital malformations. These data reflected the existing scientific literature.</p> <p>In addition, there were difficulties interpreting data collected in a registry. The results from the UK Epilepsy and Pregnancy Register had been discussed with the principal investigator, who had agreed that they should be treated with caution in view of potential confounding factors (such as the fact that use of valproate could be a marker for more severe epilepsy and more frequent tonic clonic seizures), which should be taken into account when interpreting the results.</p> <p>Sanofi was concerned that the communication to physicians proposed by the MCA could therefore be responsible for unjustified treatment decisions which might jeopardise patients' epilepsy control with even more negative consequences for the foetus.</p>
<p>2 October 2002</p>	<p>Revised wording for the Epilim SmPC was approved by the CSM. The changes were general in nature and focused on the direction that specialist advice should be obtained before women of child-bearing potential were commenced on treatment with sodium valproate. The main change was the inclusion of a new Special Warning which provided that:</p> <p style="text-align: center;"><i>“Women of child bearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic drug of choice in patients with certain types of epilepsy such as generalised epilepsy. In these women who are likely to get pregnant, specialist advice should be sought because of the potential teratogenic risk to the foetus.”</i></p> <p>The SmPC changes included a strengthening of the warning about an increased incidence of congenital abnormalities in offspring born to mothers with epilepsy, emphasising that the increased incidence related to mothers treated with sodium valproate. At that time the CSM did not suggest that a warning with regard to developmental delay should be added.</p>
<p>17 October 2002</p>	<p>Sanofi wrote back to the MCA accepting the CSM's proposed wording.</p> <p>Sanofi also proposed additional amendments to the SmPC to reflect the developing scientific literature, in line with the CSI which had been revised in August 2002, including the inclusion of the following statement:</p> <p style="text-align: center;"><i>“Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.”</i></p> <p>This statement was proposed, as a matter of caution, in order to provide physicians with information about questions raised by recent reports in the scientific literature. It was consistent both with Sanofi's understanding of the data and the MCA's own previous advice on the issue.</p>
<p>23 October 2002</p>	<p>The MCA wrote back to Sanofi, asking for data in support of this proposed statement.</p>

<p>22 November 2002</p>	<p>Sanofi replied to the MCA, submitting the requested data in support of the developmental delay statement. The developmental delay submission comprised a review of the available literature, which concluded:</p> <p><i>“Children of mothers with epilepsy exposed to AEDs in utero, have been shown in some studies to have lower scores on a variety of cognitive development measurements when compared to controls. The differences suggest that they are at greater risk for academic difficulties than control children. Maternal epilepsy and type of epilepsy (generalised versus partial), intra uterine exposure to AEDs, genetic factors, social factors such as parental education and environmental factors may all play a role in increasing the risk of developmental delay in children born to mothers with epilepsy.”</i></p> <p>One of the studies referenced in the review document submitted to the MCA was reported in a 2002 paper authored by Dean et al<sup>21</sup>. This was a retrospective study which reviewed women taking AEDs in pregnancy between 1976 and 2000. 411 potential participants were identified; 258 women were traced, and 149 participated. 211 children were exposed to monotherapy, and they were compared with 38 non-exposed siblings. The results showed developmental delay in 24% of children exposed to AEDs, against 10.5% of their non-exposed siblings. The difference was statistically significant in children exposed to carbamazepine, sodium valproate, and phenytoin, and in those exposed to more than one AED (polytherapy). The results of the study had to be interpreted with caution because of the small numbers, low response rate, and retrospective nature of the study.</p> <p>The authors concluded that</p> <p><i>“The developmental disorder is likely to have a multifactorial aetiology, but single drug therapy with valproate, phenytoin, or carbamazepine and polytherapy are all associated with a substantial risk of developmental delay, even when possible genetic factors are excluded, and a dose response effect for carbamazepine and developmental delay has been shown. The influence of an impaired mother-child interaction in the early years because of maternal epilepsy or its treatment requires further study. As discontinuation of epilepsy treatment in pregnancy because of the teratogenic risk is not usually an option, the importance of further research into susceptibility factors, the development of safer drugs, and the appropriate counselling and management of epileptic women cannot be overemphasised ».</i></p>
<p>2 December 2002</p>	<p>The MCA responded agreeing to Sanofi’s request that a warning regarding the possibility of developmental delay in children exposed to valproate during pregnancy could be included in the SmPC for Epilim. They indicated that the CSM’s Paediatric Working Group had concluded that there was now accumulating evidence to suggest a possible risk of developmental delay in infants exposed to anti-epileptics in utero, but there was conflicting evidence implicating valproate and suggested some revision to the wording proposed by Sanofi. They asked Sanofi to include a direct reference to the epidemiological studies, and proposed some additional text highlighting that neural</p>

<sup>21</sup> JCS Dean, H. Hailey, SJ Moore, DJ Lloyd, PD Turnpenny, J Little: Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth; J Med Genet, 2002; 39b (4); 251-259

	<p>tube defects are associated with total daily dose and the size of an individual dose. They proposed the following wording in relation to developmental delay:</p> <p><i>“Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment.”</i></p>
9 January 2003	Sanofi accepted the MCA’s proposal dated 2 December 2002 and submitted bulk variation applications to amend the SmPCs for the various Epilim formulations to reflect the changes.
17 March 2003	<p>The MCA provided the following wording for inclusion in Epilim PILs in relation to the risk of developmental delay in children exposed to sodium valproate during pregnancy:</p> <p><i>“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.”</i></p>
31 March 2003	<p>Sanofi sent updated PILs to the MCA, incorporating their wording in relation to developmental delay and proposing strengthened wording in relation to dosage for MCA’s approval.</p> <p>The data sheet and subsequently the SmPC for Epilim had advised, since 1993 that patients should be prescribed the lowest effective dose in divided doses because <i>“abnormal pregnancy outcome”</i> was associated with higher daily dosage and indicating that data from animal studies suggested that high plasma peak levels and high individual doses were associated with neural tube defects. Sanofi proposed that the SmPC should also include a more specific statement that: <i>“The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg per day.”</i></p>
1 April 2003	Sanofi submitted the PSUR for sodium valproate for the period 1 February 2002 to 31 January 2003. The reports of administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the CSI.
17 April 2003	The MCA, which had, by then, become the Medicines and Healthcare products Regulatory Agency (“MHRA”), wrote to Sanofi, approving the variations to the SmPC and PIL which changed the wording of the pregnancy statements.
6 May 2003	Sanofi applied to renew the marketing authorisations for the Epilim product range for a further five years.
September 2003	The MHRA published an article in its publication ‘Current Problems in Pharmacovigilance’ headed “Sodium valproate and prescribing in pregnancy” advising medical practitioners of the new data. ‘Current Problems in Pharmacovigilance’ was a drug safety bulletin that the MHRA sent to all UK doctors, pharmacists and coroners alerting them to issues concerning medicines and providing advice on ways in which medicines could be used more safely. The article stated:

	<p><i>“The risk of congenital malformations in infants born to mothers receiving anti-epileptic medication 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 mothers with epilepsy taking sodium valproate.</i></p> <p><i>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.</i></p> <p><i>Sodium valproate is the anti-epileptic of choice in patients with certain types of epilepsy such as generalised epilepsy with or without myoclonus or photosensitivity.</i></p> <p><i>Following a review of the available data including data from the UK Pregnancy and Epilepsy Register, CSM has advised the following:</i></p> <p><i>Women of childbearing potential should not be started on sodium valproate without specialist neurological advice.</i></p> <p><i>Women taking sodium valproate who are likely to become pregnant should receive specialist advice because of the potential teratogenic risk to the foetus.</i></p> <p><i>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 release preparation.</i></p> <p><i>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.”</i></p> <p>The article itself, and informed commentary on it, made clear that Epilim remained a first line treatment choice for patients with certain types of epilepsy, but reiterated the warnings in relation to pregnancy. It confirmed, in accordance with the revised SmPC, that women who might become pregnant should seek specialist advice and it encouraged the use of folate supplements and treatment with monotherapy in pregnancy.</p>
<p>October 2003</p>	<p>The National Institute for Health and Clinical Excellence (NICE) issued Technology Appraisal Guidance (TAG) on use of newer AEDs in adults. The NICE Guidance recommended the continued prescription of the older treatments, including sodium valproate. It stated at paragraph 4.3.8 of the TAG that:</p> <p><i>“The Committee noted that the issue of whether antiepileptic drugs may be harmful to the unborn child if taken during pregnancy is a major concern. The Committee specifically took note of the particular concern regarding the risks to the unborn child associated with the use of sodium valproate, and that, because of this, the Summary of Product Characteristics for sodium valproate (Epilim) warns that, for partial seizures, sodium valproate should be used in</i></p>

	<p><i>women only if they are resistant to other treatments. The experts advised the Committee that despite the concerns highlighted in the Summary of Product Characteristics, sodium valproate may be an appropriate choice for women of childbearing age with some types of generalised seizures, provided that an informed choice has been made. The Committee was persuaded that, as yet, there are few data upon which to base a robust assessment of the risks to the unborn child associated with newer drugs.”</i></p> <p>The NICE Guidance effectively restated what was known about sodium valproate at the time and used it as a context in which to place the newer drugs. The TAG supported the continued use of sodium valproate in women of childbearing age with generalised seizures, in appropriate cases and following counselling. NICE’s review provided further independent confirmation that Sanofi’s assessment of the latest evidence remained up to date and accurate.</p>
5 November 2003	The MHRA wrote to Sanofi, confirming that it considered the wording of the SmPC to be satisfactory.
March 2004	<p>Following the publication of a meta-analysis by Fried et al.<sup>22</sup> Sanofi considered the extent to which epilepsy itself represented a risk factor for malformations.</p> <p>This meta-analysis reviewed those studies investigating the occurrence of major malformation rates among children born to women with epilepsy both treated and untreated and non-exposed children of mothers who did not have epilepsy. It concluded that, while there were a number of studies that showed epilepsy to be a risk factor, these tended to be the smaller studies and the finding may have been due to publication bias. The authors acknowledged that the data selected for their study had limitations and that further research was needed. They noted in particular that type and severity of epilepsy (about which information was not available in most studies selected) could potentially influence outcomes: the untreated women were likely to have milder forms of epilepsy, whereas women with severe forms were more likely to be on one or more AEDs. Overall, however, the study called into question the commonly held view that epilepsy by itself represents a teratogenic risk.</p>
April 2004	<p>Sanofi sent MHRA a copy of a paper presented by Professor Gus Baker (a member of Professor Chadwick’s group) at a symposium in Liverpool that reported on the results of a retrospective study investigating neuropsychological measures in children exposed to AEDs in utero.</p> <p>The paper presented by Professor Baker was not peer reviewed and Sanofi advised MHRA that copies of the published papers reporting on this study would be provided once these were available. (The study was published in November 2004, see below)</p>
12 May 2004	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate including all available literature for the period 1 February 2003 – 31 January 2004. The reports of

<sup>22</sup> Fried S et al. “Malformation rates in children of women with untreated epilepsy. A meta-analysis”. Drug Safety March 2004; 27(3): 197-202

	administration during pregnancy did not result in a requirement for amendment of the information in the relevant section of the CSI.
28 May 2004	The Epilim marketing authorisations were renewed.
19 July 2004	<p>Dr Adab co-authored a Cochrane Review: 'Common antiepileptic drugs in pregnancy in women with epilepsy'.<sup>23</sup> Cochrane reviews are systematic reviews of available evidence regarding research questions, which aim to minimise bias and produce reliable findings to inform decision-making. They are highly regarded and influential.</p> <p>This Cochrane Review considered all the studies published between 1966 and December 2003, assessing the <i>“limited evidence about which specific drugs carry more risk than others to the neurodevelopment of children exposed in utero”</i>. The Review found that there were very few studies on exposure to sodium valproate, and failed to identify a detrimental effect with other older AEDs (carbamazepine and phenytoin) in monotherapy. It concluded that:</p> <p><i>“Based on the best current available evidence it would seem advisable for women to continue medication during pregnancy using monotherapy at the lowest dose required to achieve seizure control. Polytherapy would seem best avoided where possible. More population based studies adequately powered to examine the effects of in utero exposure to specific monotherapies which are used in everyday practice are required”</i>.</p>
July 2004	<p>Professor Chadwick and Dr Adab’s further study on developmental delay was accepted for publication in the Journal of Neurology, Neurosurgery &amp; Psychiatry (it was published in November 2004)<sup>24</sup>. The study was based on retrospective data, as the first paper<sup>25</sup> had been, but instead of responding to postal questionnaires the mothers and their children underwent clinical assessment in the form of a “semi-structured” interview by a clinician, and medical records were reviewed to confirm information. According to the paper 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. Average (mean) verbal IQ was significantly lower in the sodium valproate group compared to unexposed and other monotherapy groups. Multiple regression analysis to adjust for other confounding factors showed that both sodium valproate exposure and frequent tonic-clonic seizures in pregnancy were significantly associated with a lower verbal IQ. There was a significant negative correlation between dysmorphic features and verbal IQ in children exposed to sodium valproate but the study showed no statistically significant difference between sodium valproate and other AEDs on measures other than verbal IQ. The authors commented that as the data were retrospective their results needed to be interpreted with caution. In terms of practical conclusions to be drawn from the study, the authors recommended that women with epilepsy needed careful counselling about the individual risks and benefits</p>

<sup>23</sup> Adab N et al., Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev. 2004; (3):CD004848.; online version published 19 July 2004

<sup>24</sup> Adab et al. The longer term outcome of children born to mothers with epilepsy J Neurol Neurosurg Psychiatry 2004; 75: 1575-1583

<sup>25</sup> N Adab, A Jacoby, D Smith, D Chadwick: Additional educational needs in children born to mothers with epilepsy: J Neurol Neurosurg Psychiatry 2001;70:15-21

	<p>of AED treatment before pregnancy. They considered that the study identified sodium valproate as a drug carrying potential risks for developmental delay and cognitive impairment and that frequent tonic-clonic seizures had a similar effect.</p> <p>Sanofi concluded that this publication justified the inclusion of a statement, as a matter of caution, in the SmPC even if, in view of the multifactorial causes of developmental problems and the methodological shortcomings of the study, Sanofi, like the authors, did not consider that the data established a causal association. The CSI was updated in October 2004 to refer to the data on reduced verbal IQ and applications were made to the MHRA in November 2004 to revise the product information (SmPCs and PILs).</p> <p>The following statement was subsequently approved by the MHRA in the SmPC:</p> <p><i>“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”.</i></p>
October 2004	<p>The CSI was updated in October 2004 to reflect this new publication. Indeed, Sanofi concluded that this new publication justified the inclusion of a statement, as a matter of caution, in the SmPC even if, in view of the multifactorial causes of developmental problems and the methodological shortcomings of the study, Sanofi, like the authors, did not consider that the data established a causal association.</p>
October 2004	<p>NICE published a Clinical Guideline on ‘The diagnosis and management of the epilepsies in adults and children in primary and secondary care’ (CG20)<sup>26</sup>. This contained detailed advice on many aspects of the treatment of epilepsy, but Appendix B focused on pharmacological treatment. It confirmed that sodium valproate was a first line drug treatment for all listed seizure types (Table 1 of Appendix B) and all but one (the exception being infantile spasms) of the epilepsy syndromes listed (Table 2 of Appendix B). Appendix B highlighted the CSM advice published in Current Problems in Pharmacovigilance in 2003 that: <i>“women of child bearing potential should not be started on sodium valproate without specialist advice”</i>. The main text of the Guideline emphasised at paragraph 4.11.4A the need for counselling:</p> <p><i>“In women of childbearing potential, the risk of the drugs...causing harm to an unborn child should be discussed and an assessment made of 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 to the unborn child.”</i></p>
November 2004	<p>Sanofi submitted an application to the MHRA to vary the marketing authorisations for Epilim products to include a new statement in the SmPC recommending that:</p> <p><i>“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</i></p>

<sup>26</sup> NICE Clinical Guideline: The epilepsies - The diagnosis and management of the epilepsies in adults and children in primary and secondary care 2004 (CG20)

	<p><i>Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks”.</i></p> <p>Similar information was proposed for the revised PIL.</p> <p>Following this submission, the MHRA asked Sanofi to restructure the Epilim PIL and stated that the pregnancy statement in the PIL:</p> <p><i>“...should start off with a statement along the lines that the doctor should discuss the problems that may arise if Epilim is used in pregnancy before they start treatment and then clearly spell out the potential teratogenic and post-natal effects in user-friendly language.”</i></p> <p>The MHRA also suggested that it would be better to set out information on birth defects in bullet points, and to:</p> <p><i>“state that if the patient becomes pregnant or think they may be pregnant during treatment they should tell the doctor immediately and if planning to become pregnant that they should not do so until they have discussed this with their doctor.”</i></p>
<p>12 May 2005</p>	<p>Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2004 – 31 January 2005. Including all relevant literature. This was a routine submission for Epilim authorisations. From the reports of exposure during pregnancy collected during the reference period, no new relevant information was identified. No update to the CSI was made as a result of this PSUR.</p>
<p>September 2005</p>	<p>The first findings from the UK Epilepsy and Pregnancy Registry were published as an abstract in the online <i>J Neurol Neurosurg Psychiatry</i><sup>27</sup>, using information gathered between December 1996 and March 2005.</p> <p>The authors reported that almost 96 per cent of babies born to women with epilepsy had no major congenital malformations (MCM). They also found that the MCM rate was significantly greater in those pregnancies where the child was exposed only to sodium valproate (6.2% ; 95% C.I. 4.6 - 8.2) compared with those exposed only to carbamazepine (2.2% ; 95% C.I. 1.4 - 3.4)(OR 2.78 [p&lt;0.001]; adjusted OR 2.97 [p&lt;0.001]). There were also fewer MCMs reported in children exposed only to lamotrigine (3.2%; 95% C.I. 2.1 - 4.9) compared with those exposed only to sodium valproate OR 0.52 [p=0.015]; although the difference was not statistically significant and the risks of sodium valproate and lamotrigine overlapped. While there was a trend towards more MCMs with increasing doses of sodium valproate this was not significant, whereas there was a significant dose-response relationship with lamotrigine. The study results also showed that risks of a baby being born with MCMs were increased if the mother was taking more than one AED (polytherapy), and if one of the polytherapy drugs was sodium valproate.</p>

<sup>27</sup> J Morrow, A Russell, E Guthrie, L Parsons, I Robertson, R Waddell, B Irwin, R C McGivern, P J Morrison, J Craig. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77: 193-198

	<p>The product's SmPC already included a warning about the possible risk of MCMs, so no immediate changes were required.</p> <p>A preliminary analysis<sup>28</sup> of data from the Neurodevelopmental Effects of Antiepileptic Drugs ("NEAD") study was also published in 2005. The data on serious adverse neurodevelopmental outcomes suggested that such outcomes occurred in 10% of carbamazepine, 2% of lamotrigine, 12% of phenytoin, and 24% of sodium valproate exposed children. The NEAD study was ongoing, but the authors considered that the preliminary results raised concerns over the use of sodium valproate as a first-line treatment in women of childbearing potential. The authors stated that they did not consider that the results of this and other studies meant that sodium valproate should never be used in women of child bearing potential; they offered the opinion that sodium valproate is an excellent AED, and may in some cases be the only treatment that can control the patient's epilepsy. They emphasised, however, that sodium valproate should not be used to treat women of childbearing potential without consideration of the possible risks to children conceived in future, and discussion of these risks with the patient.</p>
15 October 2005	<p>The applications to amend the data sheets for Epilim were approved by the regulatory authority to incorporate the following wording:</p> <p><b>Pregnancy:</b></p> <p>Women of childbearing potential should not be started on Epilim without specialist neurological advice.</p> <p>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> <p><b>Use during pregnancy and lactation:</b></p> <p>Women of childbearing potential should not be started on Epilim without specialist neurological advice.</p> <p>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.</p> <p>Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate. When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")</p>

<sup>28</sup> Meador K, Loring DW, Baker G, Clayton Smith J, Pennell P, Liporace J, Kalayian L, Kini U, and the NEAD Study Group. Differential and Dose Dependent Effects of In Utero Antiepileptic Drugs. Neurology 2005;64 (Suppl 1):A427

	<p><b>4.6.1 Pregnancy</b></p> <p>From experience in treating mothers with epilepsy, the risk associated with the use of Epilim during pregnancy has been described as follows:</p> <p><b>- Risk associated with epilepsy and antiepileptics</b></p> <p>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.</p> <p>Malformations most frequently encountered are cleft lip and cardio-vascular malformations.</p> <p>Epidemiological studies have suggested an association between in-utero exposure to Epilim and a risk of developmental delay. Developmental delay has been reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.</p> <p><b>- Risk associated with valproate</b></p> <p>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</p> <p>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</p> <p>In humans: Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in offspring born to mothers with epilepsy treated with valproate.</p> <p>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.</p>
<p>25 July 2008</p>	<p>Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2006 – 31 January 2007. This was a routine submission in respect of the Epilim marketing authorisations. A cumulative review on autism, autism spectrum disorders (ASD) and Asperger’s syndrome was performed, from the reports of exposure during pregnancy. The conclusions were: <i>“According to the National Center for Health Statistics, the prevalence of autism ranges from around 10 to 15 cases per 10,000 populations. It is noteworthy that a statement is present in the CSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient. No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company”.</i></p>

7 October 2008	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2007- 31 January 2008. This was a routine submission in respect of the Epilim marketing authorisations. A cumulative review on autism, autism spectrum disorders (ASD) and Asperger’s syndrome was performed, from the reports of exposure during pregnancy. The conclusions were: <i>“According to the National Center for Health Statistics, the prevalence of autism ranges from around 10 to 15 cases per 10,000 populations. It is noteworthy that a statement is present in the CCSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient. No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company”</i> .
December 2008	Publication of a paper (Bromley et al <sup>29</sup> ) which reported preliminary results of a prospective study being undertaken by the Liverpool Group. These data suggest an increased incidence of autism spectrum disorders in children who had been exposed to valproate in utero as compared with a control group.
23 April 2009	<p>Sanofi submitted an application for a marketing authorisation variation to the MHRA to update the SmPC to, include a warning that autism spectrum disorders had been reported in children exposed to valproate in utero. This application was based on a cumulative review of the safety data collected in Sanofi’s global electronic pharmacovigilance database and a review of the scientific literature. The conclusion of the review was that some data were available on autism in children after maternal exposure to valproate but there was currently limited information in relation to a causal relationship</p> <p><i>“Section 4.4</i>  <i>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).</i></p> <p><i>Precautions: Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).</i></p> <p><i>Section 4.6</i></p>

<sup>29</sup> Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology 2008; 71(1-2): 1923-1924

*Women of childbearing potential should not be started on Epilim without specialist neurological advice.*

*Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (See also section 4.6.1). Women who are taking Epilim and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks.*

*Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment.*

*If pregnancy is planned, consideration should be given to cessation of Epilim treatment, if appropriate.*

*When Epilim treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled "In view of the above")*

*Risk associated with epilepsy and antiepileptics*

*In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.*

*No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.*

*Antiepileptic drugs should be withdrawn under specialist supervision.*

*Risk associated with valproate*

*In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.*

*There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.*

*In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.*

*Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.*

*Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such*

	<p><i>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.</i></p> <p><i>In view of the above data</i></p> <p><i>When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy.</i></p> <p><i>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.</i></p> <p><i>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.</i></p> <p><i>During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk.</i></p> <p><i>Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).</i></p> <p><i>Risk associated with seizures</i></p> <p><i>During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular Risk of death for mother and the unborn child.</i></p> <p>The variation was approved on 1 October 2010.</p>
April 2009	<p>A referral to the EMA's Committee for Medicinal Products for Human Use ("CHMP") under Article 31 of Directive 2001/83/EC was initiated by the Netherlands regulatory authority because of concerns relating to the efficacy of using valproate containing medicinal products in the acute treatment of manic episodes and the prevention of recurrence of mood episodes in patients with bipolar disorder.</p>
August 2010	<p>CHMP Referral was ended in August 2010 (EC Decision) with the following outcome: Positive benefit-risk ratio in the indication "<i>Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to the medicinal product for acute mania</i>" subject to amendments to the Product Information.</p>

<p>12 November 2010</p>	<p>Sanofi's application for a variation to update the SmPC for Depakote in line with the Article 31 referral outcome from 26 August 2010 (see above) was approved.</p>
<p>7 June 2011</p>	<p>The CSI was reviewed in February 2011. The teratogenic risk of valproate was already described in the CSI. Additionally, the EU Pharmacovigilance Working Party (PhVWP) had recommended that "valproate containing medicinal products 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)" and they recommended use of effective contraception during treatment. Therefore, in the context of the update of the CSI, Sanofi considered that the prevention of the risk of congenital abnormalities would be strengthened by adding the use of contraception associated with valproate administration in women of child-bearing potential.</p> <p>Sanofi subsequently submitted an application to the MHRA on 7 June 2011 to update the SmPC in line with revisions to the CSI. This update adapted the wording in section 4.4. and 4.6., and added reference to use of effective contraception during treatment:</p> <p><u><i>"Section 4.4</i></u>  <u><i>Women of childbearing potential (see section 4.6): This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Epilim is prescribed for the first time, or when a women (sic) of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.</i></u></p> <p><u><i>Section 4.6 - Update below categories and the remaining text remains as it is.</i></u>  <u><i>Risk associated with valproate</i></u>  <i>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</i>  <i>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</i>  <i>In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.</i>  <i>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.</i>  <i>Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that</i></p>

	<p><i>antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy. Autism spectrum disorders have also been reported in children exposed to valproate in utero.</i></p> <p><u><i>In view of the above data</i></u>  <i>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 (sic) of child bearing potential treated with Epilim plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.</i></p> <p><i>If a women (sic) plans a pregnancy or becomes pregnant, Epilim therapy should be reassessed whatever the indication:</i></p> <ul style="list-style-type: none"> <li><i>• In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Epilim treatment is to be continued during pregnancy, it is recommended to use Epilim in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.</i></li> <li><i>• In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.</i></li> <li><i>• Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.</i></li> </ul> <p><i>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.</i></p> <p><i>Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use).</i></p> <p>The variation was approved on 3 July 2011.</p>
<p>24 August 2012</p>	<p>Sanofi submitted an application to the MHRA to update the SmPC in line with revised CSI. This update added reference to dose – effect for congenital malformations.</p> <p>This update to the CSI was based on a safety review carried out by Sanofi to evaluate the incidence of congenital malformations reported for valproate and to assess a dose-effect of valproate administered during pregnancy and the occurrence of congenital malformations.</p> <p>A search on the incidence of congenital malformations and valproate was performed from the published articles from registries and cohort studies on pregnant women with epilepsy until 24 May 2012. Results of this systematic literature review suggest that</p>

the overall incidence of congenital malformations in children born of women with epilepsy is approximately threefold that of healthy women. The risk is elevated for all AED monotherapy and further elevated for AED polytherapy compared to women without epilepsy. The risk was significantly higher for children exposed to valproate monotherapy and to polytherapy of 2 or more drugs when the polytherapy combination included phenobarbital, phenytoin, or valproate. It concluded that further research is needed to delineate the specific risk for each individual AED and to determine underlying mechanisms including genetic risk factors.

To examine the dose effect of valproate, a review of the worldwide literature and the global Sanofi pharmacovigilance database was undertaken.

From analysis of the Sanofi pharmacovigilance database, although the daily dose was unknown in 35% of cases of malformations, a dose-effect of valproate on congenital malformations was evidenced from the cases of congenital malformations retrieved in the global Sanofi pharmacovigilance database.

	<p>The review of the available literature sources undertaken<sup>30 31 32 33 34 35 36 37 38 39 40 41 42 43</sup> also supported this dose effect.</p> <p>Results from this review therefore indicated that there was sufficient evidence to conclude that the teratogenic effect of valproate is dose-dependent.</p> <p>As a result of this review, the CSI was updated to add the following statement:</p> <p><i>“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.”</i></p> <p>Section 4.6 of the SmPC was updated accordingly:</p> <p><u><i>“Section 4.6 - Update below categories and the remaining text remains as it is.</i></u></p>
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<sup>30</sup> Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology*. 2005;64(6):961-5

<sup>31</sup> Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry*. 2006;77(2):193-8

<sup>32</sup> Bromfield EB, Dworetzky BA, Wyszynski DF, Smith CR, Baldwin EJ, Holmes LB. Valproate teratogenicity and epilepsy syndrome. *Epilepsia*. 2008; 49(12):2122-4.

<sup>33</sup> Lindhout D, Omtzigt JG, Cornel MC. Spectrum of neural-tube defects in 34 infants prenatally exposed to antiepileptic drugs. *Neurology*. 1992; 42(Suppl. 5):111-8.

<sup>34</sup> Omtzigt JG, Los FJ, Grobbee DE, Pijpers L, Jahoda MG, Brandenburg H, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology*. 1992;42(Suppl. 5):119-25

<sup>35</sup> Koch S, Lösche G, Jager-Romän E, Jakob S, Rating D, Deichl A, et al. Major and minor birth malformations and antiepileptic drugs. *Neurology*. 1992; 42(Suppl. 5):83-8.

<sup>36</sup> Samrén EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, 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):981-90

<sup>37</sup> Samrén EB, van Duijn CM, Christiaens GC, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol*. 1999;46(5):739-46

<sup>38</sup> Kaneko S, Battino D, Andermann E, Wada K, Kan R, Takeda A, et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res*. 1999; 33(2-3):145-58.

<sup>39</sup> Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. *Seizure* 2002; 11(8): 512-8.

<sup>40</sup> Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol*. 2006; 13(6):645-54.

<sup>41</sup> Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate: evidence of dose relationship in teratogenic effect. *CNS Drugs* 2008; 22(4): 325-34.

<sup>42</sup> Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, et al; American Academy of Neurology; American Epilepsy Society. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009; 50(5): 1237-46.

<sup>43</sup> Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011; 10(7):609-17.

	<p><u><i>Risk associated with valproate</i></u>  <i>In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.</i>  <i>There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.</i>  <i>In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers treated with valproate.</i>  <i>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. <b>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.</b></i>  <i>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.</i></p> <p><i>Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.</i></p> <p><i>Autism spectrum disorders have also been reported in children exposed to valproate in utero”.</i></p> <p>The variation was approved on 28 November 2012.</p>
<p>October 2013</p>	<p>MHRA made a referral under Article 31 of Directive 2001/83/EC for valproate for the treatment of epilepsy. The referral letter stated:</p>

	<p>Epilepsy is a serious neurological condition and it is important that it is treated effectively including during pregnancy. It is widely recognised that women who take antiepileptics during pregnancy have a higher risk of having a child with a birth defect than women in the general population - this risk is estimated to be 2-3 times higher. The likelihood of having a child with birth defects is further increased if the woman takes more than one antiepileptic medicine during pregnancy. 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 with some of the other antiepileptic drugs. This risk is clearly reflected in the valproate product information provided for patients and prescribers. The UK product information also contains some information on the association between foetal valproate exposure and longer term neurodevelopmental delay in the child, including a link with autism spectrum disorder.</p> <p>In 2009, there was also a European review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder. This review considered the teratogenic risk associated with use of valproate in pregnant women and also examined the potential for delayed intellectual development in the child. At this time it was not clear whether adverse neurodevelopmental effects would improve with time or be more enduring or what the gravity of impact of various maternal confounders might be on the observed increased risk and this uncertainty remains reflected in the current information in many member states, including the UK.</p> <p>In recent years, results of further studies have emerged which have improved our understanding and allow us to better characterise the risk of the longer term potential neurodevelopmental effects following <i>in utero</i> exposure to valproate. These studies have highlighted that in some children the effects appears to persist and manifest as a range of neurodevelopmental abnormalities and autism spectrum disorder. These emerging data also suggest that the risk of neurodevelopmental delay and autism spectrum disorder may be independent of maternal confounders<sup>1-4</sup>.</p> <p>Product information appears to differ across the European Union and there is a need for further revisions in order to bring it in line with all currently available evidence. The most recent data on neurodevelopmental delay and autism spectrum disorder associations with foetal valproate syndrome also call for a re-evaluation of the benefit risk of valproate where safer alternative treatments are available in particular in relation to use in migraine prophylaxis and bipolar disorder management.</p> <p>Whilst there are existing warnings in the valproate product information it is not considered to fully reflect the most recent evidence from the emerging studies, which have not identified a new safety concern per se but have clarified the magnitude and nature of the risk and suggest that the risk of neurodevelopmental delay is greater than previously thought. Therefore, there is a need for further review to ensure appropriate risk minimisation measures are in place to help optimise safe use and reduce the risk associated with use during pregnancy.</p> <p>In light of the above, and given widespread use of valproate in different indications, the UK considers that it is in the interest of the Union to refer valproate containing products to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether the new data impacts on the balance of benefits and risks of valproate in all of its authorised indications and whether marketing authorisations should be maintained, varied suspended or withdrawn.</p> <p>References</p> <ol style="list-style-type: none"> <li>1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kenner A, Lip race JD, Pennell PB, Privateer M, and Luing DW. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD Study): a prospective observational study. <i>Lancet Neurology</i>. 2013, March;12(3): 244-252.</li> <li>2. Bromley R et al. The prevalence of neurodevelopment disorders in children prenatally exposed to antiepileptic drugs. <i>J Neural Neurosurgery Psychiatry</i> 2013; 0: 1-7</li> <li>3. Christensen J et al. Association of sodium valproate with Risk of Autism Spectrum Disorders and Childhood Autism. <i>JAMA</i>, April 24, 2013. Vol 309, No 16.</li> <li>4. Veiby, Gyri et al. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. <i>Epilepsia</i>. 2013. Aug; 54(8): 1462-72</li> </ol>
9 October 2014	<p>The Article 31 referral concluded with a finding by the Pharmacovigilance and Risk Assessment Committee (“PRAC”) that the benefit-risk balance of valproate remained favourable subject to the conditions to the marketing authorisations, and taking into account the amendments to the product information, where applicable, and other risk minimisation measures recommended.</p>

<p>10 October 2014</p>	<p>EMA Press release following the Article 31 referral:</p> <p><i>“PRAC recommends strengthening the restrictions on the use of valproate in women and girls Women to be better informed of the risks of valproate use during pregnancy</i></p> <p><i>The EMA’s Pharmacovigilance and Risk Assessment Committee (PRAC) has 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.</i></p> <p><i>Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option after trying other treatments, should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions. Women who have been prescribed valproate should not stop taking their medicine without first consulting their doctor.</i></p> <p><i>In countries where valproate medicines are authorised for the prevention of migraine, women must not use valproate for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.</i></p> <p><i>The PRAC also recommended that doctors who prescribe valproate provide women with full information to ensure understanding of the risks and to support their decisions.</i></p> <p><i>These recommendations follow a review of available data on the effects of valproate exposure during pregnancy. During the review the PRAC also consulted representatives of patients and families who have been affected as well as a group of experts and specialists. While valproate remains an option for patients where other treatments have failed or are not tolerated, the Committee concluded that women and healthcare professionals need to be better informed about the risks of valproate exposure in the womb and of the need for effective contraception.</i></p> <p><i>Recent studies have shown a risk of developmental problems of up to 30 to 40% in 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.</i></p> <p><i>In addition, data show that 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 to a 2 to 3% risk for children in the general population. Available data also show that children exposed to valproate in the womb are 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).</i></p>
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	<p><i>The PRAC recommended that educational materials should be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks. Doctors will be required to review the treatment of girls and women on a regular basis, including at puberty and when a woman plans to become pregnant. The PRAC emphasised that women should not stop taking valproate without first consulting their doctor.</i></p> <p><i>The EU product information for healthcare professionals and patients is to be updated with the latest information and recommendations.</i></p> <p><i>The recommendations of the PRAC will now be sent the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. In the meantime, women currently taking valproate who have any questions about their treatment should speak with their doctor”.</i></p> <p>MHRA Press Release:</p> <p><i>“The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended strengthening the restrictions on the use of valproate medicines due to an increased risk of birth defects and developmental problems in children exposed to valproate in the womb.</i></p> <p><i>It is being recommended that valproate medicines should not be used to treat epilepsy and bipolar disorder in girls, women who can become pregnant or pregnant women unless other treatments are ineffective or not tolerated.</i></p> <p><i>The recommendations will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for a final opinion. We will provide further information to patients and healthcare professionals once a final opinion is reached.</i></p> <p><i>Dr. Sarah Branch, Deputy Director of MHRA’s Vigilance and Risk Management of Medicines division said: “There are already strong warnings contained in product information for patients and prescribers on the potential for birth defects and developmental disorders in children born to women taking valproate during pregnancy. It is now being recommended that this information is strengthened further. “It is important that anyone taking valproate should not stop their treatment without first discussing it with their doctor. “If anyone has any questions they should speak with their GP or pharmacist.”</i></p>
November 2014	<p>Publication of Cochrane Review: “Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child”<sup>44</sup></p> <p>This Cochrane Review considered all the studies published up to May 2014 and aimed to assess whether exposure to antiepileptic drugs (AEDs) during pregnancy is linked to poorer levels of ability for skills such as IQ, language and memory (neurodevelopment).</p> <p>The authors stated that the most important finding was the reduction in IQ in the VPA exposed group. However, the Review noted that, for some women, valproate was the</p>

<sup>44</sup> Bromley R1, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014 Oct 30;(10):CD010236

	<p>most effective drug at controlling seizures. The authors stated that informed treatment decisions required detailed counselling about these risks at treatment initiation and at pre-conceptual counselling. They observed that insufficient data were available in relation to newer AEDs, some of which were commonly prescribed, and that further research is required. Finally, they concluded that most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carry a maternal risk.</p>
19 November 2014	<p>The recommendations made by the PRAC were adopted by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human ("CMDh"), with minor modifications.</p> <p>These recommendations and the measures put in place are described in the response to Q11</p>
26 November 2014	<p>Sanofi sent a draft dear healthcare professional communication ("DHPC") to MHRA for review and approval. The DHPC was to be sent to neurologists, psychiatrists, general practitioners, obstetricians/gynaecologists, family planning centres, pharmacists, health visitors, midwives, school nurses, and professional associations in order to inform them of the recommendations of the PRAC and the measures that would be put in place following the Article 31 referral. Sanofi proposed that healthcare professionals should be informed that associated educational materials would be available on request from mid-January by contacting the relevant company.</p>
28 November 2014	<p>MHRA responded that the DHPC would be sent by MHRA via the Central Alerting System ("CAS") after consultation with the Commission on Human Medicines ("CHM") at the December meeting, rather than by each of the various MAHs.</p>
1 December 2014	<p>Sanofi replied to MHRA to acknowledge the arrangements and to request clarification regarding the production of educational materials as recommended by the PRAC, specifically whether this information would also be communicated by MHRA.</p> <p>MHRA confirmed that marketing authorisation holders would need to produce the necessary educational materials, but that MHRA were seeking input from stakeholders nationally on the wording and would be in touch with Sanofi with further details on the final wording and distribution. MHRA also confirmed that they planned to include links to the relevant educational materials in their DHPC.</p>
7 January 2015	<p>Sanofi submitted applications for variations to the marketing authorisations for Epilim and Depakote products to update the SmPCs to implement the PRAC recommendations. .The proposed changes for the SmPCs for Epilim products were as follows:</p> <p><u>Section 4.2:</u></p> <p><i>"Female children, female adolescents, women of childbearing potential and pregnant women</i></p> <p><i>Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully</i></p>

*reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses”.*

Section 4.4:

Removed existing text under heading “Women of childbearing potential” (see section 4.6): and added the following text in A text box.

*“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”.*

Section 4.4.2 (precautions) was unrevised from previous version

Section 4.6

*“Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.*

Pregnancy Exposure Risk related to valproate

*Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including*

*valproate is associated with a greater risk of congenital malformations than valproate monotherapy.*

*Congenital malformations*

*Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.*

*Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.*

*Developmental disorders*

*Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.*

*Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.*

*Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.*

*There are limited data on the long term outcomes.*

*Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.*

*Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).*

*Female children, female adolescents and woman of childbearing potential (see above and section 4.4)*

*If a Woman wants to plan a Pregnancy*

- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.*
- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed*
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.*

*Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:*

	<p>- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations.</p> <p>- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</p> <p>- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.</p> <p><u>Breastfeeding</u></p> <p>Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. ... (see section 4.8). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman".</p> <p>The variations were approved on 11 February 2015</p>
20 January 15	<p>MHRA sent a further email attaching the educational materials for valproate as an outcome of the Article 31 Referral, indicating:</p> <p><i>"The exact text is to be implemented. We are further exploring the utility of the Acknowledgement of Risk form as an optional support tool supplementary to GMC guidance on consent and prescribing with relevant stakeholders. We plan to issue a CAS [central alerting system], week commencing 19th Jan and will include links to the text of the HCP [healthcare professional] and Patient booklet text attached".</i></p> <p>Sanofi responded to MHRA setting out its understanding that no further activities by Sanofi or any other MAH were required to cover the distribution of these materials.</p>
21 January 15	<p>MHRA sent a copy of the link to the CAS notification to Sanofi for information. The Educational Materials (HCP and Patient Guide) were part of this CAS notification.</p>
22 April 2015	<p>Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 1 February 2012 - 23 January 2015. This was a routine submission in respect of the Epilim marketing authorisations.</p>
18 May 15 => 29 October 2015	<p>A Drug Utilisation Study ("DUS") Protocol was submitted to the EMA on 18 May 2015 on behalf of the consortium of marketing authorisation holders for valproate products, led by Sanofi. Following PRAC's comments, a revised DUS protocol and prescriber survey study protocol were submitted to PRAC on behalf of the MAHs consortium on 29 October 2015</p> <p>Note: Drug utilisation studies (DUS) describe how a medicinal product is prescribed and used in routine clinical practice in large populations.</p>
July 15 – December 15	<p>Following the distribution of the Educational Materials by the MHRA in January 2015, MHRA requested Sanofi to develop a strategy for further developing and distributing the educational materials associated with the PRAC outcomes.</p>

	<p>Following correspondence MHRA invited Sanofi to a meeting on 22 October to discuss the valproate educational materials and outcomes of a meeting with the Minister and Royal Colleges on proposals for driving forward communication of key messages in this area.</p> <p>MHRA indicated that, as part of the Article 31 review, Member States had agreed core elements for the patient and healthcare professional booklets and, in addition, a form had been drafted which was intended as an additional risk minimisation tool to provide a written record of discussions of benefits and risks of valproate between healthcare professionals and patients. The implementation of this form was to be decided by individual Member States.</p> <p>Following discussions between Sanofi and MHRA, it was agreed that Sanofi would draft more “user friendly” versions of the PRAC Educational Materials (Patient Booklet and HCP Guide). Additionally MHRA requested Sanofi to:</p> <ul style="list-style-type: none"> <li>- Produce a Patient Alert Card outlining the key risk minimisation measures</li> <li>- Add a warning to the product carton to highlight the risks associated with the use of valproate in pregnancy.</li> <li>- Produce a “Discussion of risk” form that could be used by HCPs in discussion with Patients</li> <li>- Provide a distribution plan to communicate with appropriate HCPs in the UK, and to co-ordinate the distribution of the materials for all UK Marketing Authorisation holders.</li> </ul> <p>Sanofi submitted drafts of all these materials to MHRA for review by the Valproate Stakeholder network.</p>
<p>18 December 2015</p>	<p>Sanofi met with MHRA to discuss the progress of the development of the Educational Materials</p> <p>MHRA provided feedback from a Ministerial Stakeholder meeting held on 9 December in order to bring all interested parties together for a co-ordinated approach. The meeting had been widely attended by Stakeholders from the Royal Societies, representation from neurologists, psychiatrists and pharmacy, GPs, NHS England and NICE, the Head of Electronic Prescription Alerting Services, , the MP from the All Party Working Group on Epilepsy and representatives from the Epilepsy Society. The meeting discussed the DH Alerting System and how this could best be used to communicate key messages on valproate and pregnancy to prescribers. Most current GP systems have some type of alerting system, but it was generally agreed that there is “alert fatigue” amongst professionals and most are ignored both by GPs and pharmacists.</p> <p>The draft educational materials produced by Sanofi after discussions with the MHRA in the Autumn of 2015 were discussed with the Stakeholder Group. All the proposed educational materials had been well received.</p> <p>The Royal Pharmaceutical Society had indicated that they were considering how they could be involved in the educational campaign. It was agreed by MHRA that pharmacy would be a useful route for distributing the patient card,</p>

	Other areas of discussion at the stakeholder meeting included monitoring of effectiveness of actions. The Minister had indicated that he was very keen to monitor implementation of the measures put in place and to measure effectiveness on an ongoing basis. MHRA would be looking at the Clinical Practice Research Database (“CPRD”), and Sanofi would be running the DUS and survey requested by PRAC. Additionally, the Epilepsy Association discussed re-running surveys that they have done in the past and other organisations were considering actions and would provide comments to MHRA.
January 2016	Following input from the MHRA Stakeholder groups, Sanofi worked with MHRA to finalise the UK specific educational materials – HCP and Patient Booklet, Patient Card and Discussion of Risk form. The wording was also agreed for an outer carton warning for women.
1 February 2016	Sanofi made a formal submission to the MHRA to add the agreed carton text to all UK packs.
8 February 2016	New Educational Materials were added to the eMC website and MHRA issued a Press Release on the new toolkit via CAS.  Sanofi hard copy mailing of educational materials took place between 8 and 19 February 2016, with material sent to a total of 111,460 contacts.
5 May 2016	Sanofi met with MHRA and Dr Dan Hawcutt (Royal College of Paediatrics and Child Health) to discuss child specific valproate educational materials. Dr Hawcutt indicated that he had been working closely with paediatric neurologists, particularly at Alder Hey Hospital, and he reported that the current toolkit was not being used because clinicians felt that it was inappropriate to be discussing pregnancy with pre-pubescent children and their families. He also said that it was felt that the current materials were also inappropriate for parents. Valproate is an important medicine in children and the pregnancy message is not relevant at this point in time. Materials need to be based on where the child and parent are in the process of the disease and current materials do not take this into account. He warned that the current materials would not be used as feedback he had received indicated that clinicians felt they were inappropriate for use with children.  It was agreed that RCPCH would produce draft materials and share with MHRA
20 January 2017	Sanofi made an application to MHRA to add the pictogram to the Epilim outer carton. User Testing of the Pictogram has been conducted by Sanofi and the user test report was submitted as part of the application.  This application was subsequently put on hold by MHRA to await outcome of the new Article 31 referral that was announced in March 2017.
20 January 2017	Sanofi and other companies included in the MAH consortium, submitted, in due time, -the first interim database study report of “A joint Drug Utilisation Study (DUS) of valproate and related substances in Europe using database”, for a PRAC review. The report was entitled “Evaluation of the effectiveness of risk minimisation measures: a joint PASS survey among health care professionals to assess their knowledge and attitudes on prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom”.

	<p>The preliminary conclusions were that the number of women of child-bearing potential (WCBP) using valproate (both initiation and repeat prescriptions) regardless of indication had decreased in Sweden (only 5 months data), Germany, France, Spain and UK after implementation of the risk minimisation measures (RMM). However, the preliminary data, suggested that there was no evidence of improved prescribing behaviour after implementation of the RMM, as the proportion of WCBP for whom the prescribers had considered other drugs before initiating treatment with valproate had not increased in the post-implementation period. Data also suggested a decrease in the number of pregnancies after implementation of the RMM, however no firm conclusions could be made based on the DUS data due to small numbers. It was noteworthy that the data from the joint DUS reflected only limited HCP data from involved countries, as the study was ongoing at that time. Moreover, the small sample size for indication-specific data in the post-referral period was a relevant factor to be taken into account when interpreting the results.</p> <p>In addition, a joint post authorisation safety study (PASS) HCP survey among psychiatrists, neurologists and GPs in 5 EU Member States (Germany, Spain, France, Sweden and UK) was designed to assess the effectiveness of the DHPC and educational material and, in particular, to assess whether physicians received the information, understood it and followed it when prescribing valproate. The survey had been completed by a total of 1153 physicians [...]; the results indicated that 40% of the participating HCPs stated that they did not recall receipt of either the DHPC or the educational materials. Overall, about 35% of participating HCPs in all surveyed countries did not consider that valproate should only be prescribed for WCBP in cases where other treatments were ineffective or not well tolerated. Further, only 48% of participating HCPs said that they would re-evaluate the benefit risk balance of treatment for a girl treated with valproate, when she reached puberty and only 54% of participating HCPs would re-evaluate the benefits against risks during each routine treatment review. The survey data also indicated that those HCPs who recalled the receipt of the educational materials and/or DHPC had better knowledge of the prescribing conditions for VPA. These results indicated the need to ensure adequate distribution of the materials, i.e. the receipt and recognition of the materials by all relevant HCPs, as a first step for further improvement.</p>
20 February 2017	MHRA wrote to Sanofi in relation to the impact on prescribing levels and patient awareness of the action taken since the end of the Article 31 referral as considered at a recent meeting of the valproate stakeholder network. MHRA stated that the prescribing data from CPRD showed a continuation of a steady downward trend of prescribing of valproate to women of childbearing potential over the previous few years, with the possible exception of initiations in the 11-17 age group, but that there was no evidence of an impact of the action taken to date and this, combined with anecdotal feedback from health professional representatives and patient groups, that patients were not being made aware of the risks led the meeting to conclude that further actions was required. An action plan was being drawn up.
22 February 2017	MHRA advised Sanofi that all valproate promotional materials should be submitted to them for approval prior to use.

<p>27 February 2017</p>	<p>ANSM requested to contra indicate the use of valproate products in bipolar disorder in pregnant women pending the outcome of the referral.</p> <p>MHRA informed Sanofi that they were aware of the ANSM position and were reviewing the situation for the UK.</p>
<p>9 March 2017</p>	<p>The French regulatory authority, ANSM, initiated an Article 31 referral of valproate medicines to consider the effectiveness of the risk minimisation measures put in place following the 2014 referral and to consider whether further EU-wide action should be recommended to minimise the risks in women who are pregnant or of childbearing age.</p>
<p>24 May 2017</p>	<p>Preliminary assessment reports from the PRAC Rapporteur and Co-Rapporteur were received by Sanofi, with updated reports received on 6 June 2017.</p>
<p>26 September 2017</p>	<p>The EMA held a Public Hearing to consider valproate, which asked: Based on your experience with valproate treatment during pregnancy:</p> <ul style="list-style-type: none"> <li>• Question 1: What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?</li> <li>• Question 2: What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?</li> <li>• Question 3: What other measures should be taken to reduce the risks of using valproate during pregnancy?</li> </ul> <p>Sanofi attended this Public Hearing and contributed as one of the MAHs for valproate products.</p>
<p>4 October 2017</p>	<p>A summary of the Public Hearing was published by the EMA</p> <ol style="list-style-type: none"> <li>1. The testimony indicated that the risks of use of valproate in pregnancy were undeniable and well characterised. The views of the families and others on the seriousness of these and their impact on those affected had been powerfully and movingly conveyed to the PRAC.</li> <li>2. Most speakers had confirmed that, while improved information resources had been developed in some member states after the PRAC's previous recommendations, these were still not reaching the right people at the right time. As well as communication and knowledge there was a need to think about other ways to effect change.</li> <li>3. Speakers had provided important ideas, thoughts and suggestions about how dissemination of information could be improved including: <ul style="list-style-type: none"> <li>• Application of a visible reminder of the risks on the outer packaging of valproate medicines</li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>• Ensuring that every time valproate was dispensed, women receive it in appropriate packaging accompanied by information and discussion of the risks</li> <li>• Alert prompts embedded in prescribing and dispensing software, to ensure the risks and the need for a discussion with patients were always flagged to healthcare professionals at the point of care</li> <li>• Regular (at least annual) reviews for all women receiving long-term valproate, to ensure that their understanding of the risks and benefits was updated appropriately as their life plans change</li> <li>• A record that women had been appropriately counselled regarding valproate risks to support busy healthcare professionals in carrying out this task regularly</li> <li>• Registers of women who were receiving valproate and of children who had been exposed to valproate during pregnancy were supported</li> <li>• Further development of professional education, so that all healthcare professionals were more aware of the risks associated with valproate use in pregnancy</li> <li>• More coordinated care services at national level, to ensure individualised care plans for those affected (to the extent that the regulatory system as currently structured can influence this)</li> <li>• Public awareness campaigns</li> </ul>
<p>12&amp;13 October 2017</p>	<p>Sanofi participated in the PRAC Stakeholder group meeting where advice from SAG Psychiatry and the SAG Neurology was sought. The final PRAC assessment report indicated the following advice from these groups:</p> <p><i>“The SAG Neurology concluded that for focal epilepsies, there are a number of alternatives to valproate with either superior or similar efficacy, and valproate should not be initiated as a first-line treatment.</i></p> <p><i>For a very small proportion of genetic generalised epilepsy (GGE) about 20% of GGE patients are drug resistant/have refractory seizures became seizure free with valproate (Gesche et al, 2017)<sup>65</sup>.</i></p> <p><i>There are specific epileptic syndromes where valproate remains the most appropriate treatment as presented by Tomson and colleagues (2015)<sup>66</sup>. The SAG Neurology also confirmed that where an initiation of valproate is considered in female children and WCBP, the decision must be taken and treatment monitoring performed by a specialist (neurologist, neuro-paediatrician) experienced in the treatment and diagnosis of epilepsy. All efforts should be made to regularly re-evaluate the need of continuing VPA treatment in female children and WCBP.</i></p>

*In that respect it was an agreement that a contraindication in the treatment of epilepsy in all female patients of childbearing age would indeed hinder the optimal treatment of some epileptic patients it was not supported by the SAG experts.*

*In the cases for which it is ascertained that valproate is the only available option, the risk of generalised tonic-clonic seizures (GTCS) and sudden death from epilepsy (SUDEP) weights against the replacement/withdrawal with different AEDs. In other cases, alternatives (such as lamotrigine or leviteracetam) may be considered as safer options, which seem to have the lowest risk of overall malformation. The current data show that that there are still some prescribers that do not comply with the restricted use of the valproate in pregnant women and WCBP, and some SAG experts suggested that a stronger wording not to prescribe valproate to WCBP not using effective contraception and pregnant women could be considered.*

*The PRAC asked also the SAG experts on the best way to discontinue valproate when necessary. The SAG experts were unanimous in that there could be a disadvantage to discontinue /switch valproate during pregnancy. In other situations, current Guideline (EAN, ILAE) recommendations consider that the valproate withdrawal should be undertaken gradually (over weeks to months), but there is no evidence that could be used to recommend a specific scheme for either switch or discontinuation of valproate. Firstly, new treatment should be gradually introduced as add-on to valproate and secondly the progressive discontinuation of valproate can take place.*

*In the case of female children and WCBP a substitution early in life is recommended because this guarantees fewer difficulties (e.g. related to life choices, effects on career etc.) and less disruption of the quality of life. The experts supported the view that valproate treatment decisions must involve the patients/the carer and include a very clear communication of the risks and potential consequences to them. In patients planning pregnancy a discussion about switching valproate for another treatment, and highlighting the risks of the alternatives. For pregnant women on valproate, the experts stressed the risk of loss of seizure control may have severe maternal or foetal consequences, including death (SUDEP). The experts acknowledged the differences among the EU MSs pertaining to the treatment recommendation guidelines, dosages used, use of folates, and even ways of prescribing the medication.*

*The PRAC also consulted the SAG Psychiatry regarding the place of valproate in the treatment armamentarium for patients with bipolar disorder in clinical practice and whether there is a difference in the need for valproate with regard to the treatment of mania as compared to the maintenance after a patient treated for mania has responded to valproate. The experts were of the opinion that there is some place for valproate in bipolar disorder but not as first-line treatment. No difference in the need for valproate between the acute and the maintenance treatment phases was identified. As an additional comment, the experts pointed out that in recent years strong evidence indicated that lithium has lower reproductive toxicity than originally thought. Lithium is recommended as first-line treatment in many therapeutic guidelines, but it is still perceived in a negative manner due to its safety profile and subsequent requirements for close monitoring.*

*The experts could not identify a sub-population within the pregnant and WCBP bipolar patients where the benefits of valproate would outweigh its substantial risks.*

	<p><i>One issue that the experts highlighted was the difficulties of the definition of the effective contraception; advice from contraceptive specialists should be sought in that regard. Moreover, the experts emphasised also that adherence to the contraception is a crucial issue especially as bipolar patients in an acute manic phase are less likely to follow contraceptive advice requiring diligent (daily) adherence.</i></p> <p><i>The experts considered that effective alternative treatments that can be used during pregnancy and also in WCBP are available (i.e. pharmacological treatments and Electroconvulsive therapy - ECT).</i></p> <p><i>Regarding the discontinuation of valproate, the experts acknowledged that there are no specific recommendations for valproate switch / discontinuation and that the approach is based on clinical expertise. Some clinicians use the schedule recommended for the discontinuation for lithium as a model since it is supported by scientific data over a few weeks. The experts also highlighted difficulty in the dosage adjustments of the valproate at the time of discontinuation or treatment replacement. In the case of a pregnant patient a much faster cross-tapering can be recommended while installing the alternative treatment.</i></p> <p><i>Overall there are few scientific data on the comparative efficacy of valproate versus other drugs so that its place in the sequencing of treatments for bipolar disorder is uncertain. The panel agreed that high quality studies of the comparative efficacy of valproate and other treatments for bipolar disorder are urgently needed in order to address this important question. “</i></p>
<p>26 October 2017</p>	<p>Sanofi met with the Pharmacists Group of the EU (“PGEU”) in Brussels to discuss the role of pharmacists in communicating safety information to patients.</p>
<p>7 November 2017</p>	<p>MHRA updated Sanofi on recommendations made by the CHM Expert Working Group (“EWG”) on valproate, to contraindicate valproate in pregnant women and women of child bearing age (“WCBP”) not using an effective contraception in both bipolar disorder and epilepsy indications.</p> <p>The EWG had met during July (scene setting) and in October to review the current risk minimisation measures in place, possible reasons for lack of effectiveness and to consider further regulatory measures required to minimise the use of valproate in pregnancy. As part of their discussions, the EWG examined the PRAC rapporteur assessment reports, CPRD data and patient survey data. As a result of their meetings, they recommended that there was a need for further regulatory steps in the UK as, despite significant and repeated efforts to communicate the risk, prescribing practice has not changed significantly in women of childbearing potential and in pregnancy and patients are not fully informed (patient surveys and anecdotal feedback).</p> <p>The advice from the EWG was that:</p> <ul style="list-style-type: none"> <li>• Valproate should be contraindicated in pregnancy and in women of childbearing potential not using effective contraception.</li> <li>• This should be supported by a pregnancy prevention plan, with a requirement for pregnancy testing dependent on the method of contraception used.</li> <li>• A signed acknowledgment or consent form should be routinely used when women are reviewed.</li> </ul>

	<ul style="list-style-type: none"> <li>• A registry should be set up to record and track women taking valproate and monitor compliance with the pregnancy prevention plan</li> <li>• Changes to GP prescribing systems should support these measures</li> <li>• A pack size which supports monthly prescribing should be introduced. (MHRA indicated that there is consistent feedback that patients are receiving their medicines in plain boxes with no leaflets).</li> <li>• A pictogram, supported by appropriate user testing should be introduced.</li> </ul> <p>MHRA therefore requested that Sanofi should consider submitting an application for a variation to the UK valproate marketing authorisations to update the SmPCs in line with the EWG recommendations.</p> <p>Sanofi suggested that, as the PRAC final recommendation was expected shortly and the Article 31 referral outcome would be applicable to all EU Member States, a national decision at this stage would be premature and could lead to greater inconsistency and lack of harmonisation across the EU. Sanofi’s position was confirmed in a letter dated 23 November 2017, which followed the meeting.</p>
<p>18 December 2017</p>	<p>Sanofi met with MHRA, to provide an update of the recent stakeholder group meetings together with discussion of next steps for valproate risk minimisation measures in the UK</p> <p>MHRA indicated that the CHM were content with progress at both a national and EU level at this time, as the Article 31 referral was proceeding in a direction that was consistent with the UK position, both in terms of likely outcome of the referral and timelines for actions.</p> <p>Progress had been made towards putting actions in place to deal with the outcome of the Article 31 referral and to enabling changes in prescribing habits. MHRA was working on three work streams and discussions would be fed back to the PRAC when they received the Assessment Report in January 2018.</p> <ol style="list-style-type: none"> <li>a. Pregnancy Prevention Programme (“PPP”) and practical implications for UK clinical practice</li> <li>b. Prescribing protocols and use of the acknowledgement of risk form</li> <li>c. What the product looks like (pictogram, packaging, pack size)</li> </ol> <p>Sanofi was requested to implement item c above.</p>
<p>9 February 2018</p>	<p>PRAC Press Release issued</p> <p><i>“PRAC recommends new measures to avoid valproate exposure in pregnancy New restrictions on use; pregnancy prevention programme to be put in place</i></p> <p><i>The European Medicines Agency’s experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC) are recommending new measures to avoid exposure of babies to valproate medicines in the womb. Babies exposed are at risk of malformations and developmental problems.</i></p> <p><i>What are the main measures recommended by the PRAC?</i></p> <ul style="list-style-type: none"> <li>• <i>Where licensed for migraine or bipolar disorder:</i></li> </ul>

– In pregnancy - valproate must not be used.  
 – In female patients from the time they become able to have children – valproate must not be used unless the conditions of a new pregnancy prevention programme (see below) are met.

• For epilepsy:  
 – 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.

*What are the main points of the new valproate pregnancy prevention programme?*

- 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.

*Medicines containing valproate have been approved nationally in the EU to treat epilepsy, bipolar disorder and in some countries for prevention of migraine. They are known to pose a considerable risk of malformations and developmental problems in babies who are exposed to valproate in the womb. An earlier review had recommended measures aimed at better informing women about these risks in order to reduce use of the medicine during pregnancy, and not starting treatment unless other options were ineffective or could not be used because of side effects. The current review was launched because of concerns that these measures had not been sufficiently effective.*

*The PRAC examined the available evidence and consulted widely with healthcare professionals and with patients, including women and their children who have been affected by valproate use during pregnancy, through written submissions, expert meetings, meetings with stakeholders including healthcare professionals, patient organisations, patients and their families, and via a public hearing. The PRAC noted that women were still not always receiving the right information in a timely manner and that further measures were needed to help avoid use during pregnancy. However, it was also*

	<p><i>clear that for some women, such as those with particular forms of epilepsy, valproate is the only appropriate treatment and might be life-saving. The PRAC therefore considered that the way the products are used should be changed. It recommended strengthening restrictions on their use and introducing new measures to require appropriate counselling and information for affected women.</i></p> <p><i>The PRAC also recommended that the companies marketing these medicines carry out additional studies to further characterise the nature and extent of the risks posed by valproate and to monitor ongoing valproate use and the long-term effects from affected pregnancies.</i></p> <p><i>Because valproate medicines are all licensed at national level, the PRAC recommendations will now be sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human1 (CMDh), which will adopt a position.</i></p> <p><i>In the meantime, women who have any concerns should consult their doctor. Women and girls who have been prescribed valproate should not stop taking their medicines without consulting their doctor as doing so could result in harm to themselves or to an unborn child”.</i></p>
<p>23 February 2018</p>	<p>Sanofi met with MHRA to consider how the recommendations of the PRAC and the new risk minimisation measures could be implemented in the UK as quickly as possible.</p> <p>There had been a valproate stakeholder network meeting on 22 January 2018 and the CHM Expert Working Group on valproate had also met at the end of January. Both these groups had discussed the implementation of the PRAC recommendations and, in particular, the provision of adequate information to female patients, including the implementation of the Pictogram on packs.</p> <p>Sanofi provided an update on progress:</p> <ul style="list-style-type: none"> <li>• <b>Pictogram and Carton Warning</b> Mock ups were close to finalisation and would be submitted to MHRA by 2 March. These would be implemented into production as soon as possible – dates to be provided to MHRA for different packs by 2 March.</li> <li>• <b>Pictogram on Primary Packaging</b> MHRA’s primary concern was to ensure that the pictogram was seen by patients. In view of the possibility that original packs could be split at pharmacy level, the inclusion of the pictogram on primary packaging might be the option.</li> <li>• <b>Pack size</b> MHRA asked Sanofi to provide timelines for the introduction of a new pack size by 27 February with a preference for packs of 30 rather than 60 tablets.</li> </ul> <p>As an interim measure pending introduction of the new pack size, arrangements needed to be put in place to ensure that all women received the pictogram with the associated warning message, the PIL and the Patient Card. It was agreed that pharmacists should be directed to the electronic medicines compendium to download a copy of the latest PIL whenever they dispense valproate and that Sanofi should</p>

	<p>provide patient cards and a sticky dispensing label to pharmacists to use. (MHRA would issue such instructions to pharmacists on this point via the Royal Pharmaceutical Society).</p> <ul style="list-style-type: none"> <li>• <b>Dispensing Label</b> Sanofi agreed to develop stickers with the pictogram and warning text on for pharmacists to use when dispensing in a white box. Sanofi agreed to provide mock-up of stickers to MHRA for review by 9 March.</li> <li>• <b>Educational Materials</b> MHRA requested that Sanofi submit mock ups of the Patient Card by 9 March and the Patient and HCP booklet by 16 March, so that these materials could be ready as soon as the Article 31 referral was concluded. MHRA also wished to share these materials with their stakeholder group.</li> <li>• <b>Variation Submissions</b> MHRA requested that Sanofi prepare these for submission on 22 March.</li> <li>• <b>Registry</b> Sanofi were asked to consider and make proposals to MHRA for a Pregnancy Registry to answer the question “what proportion of the WOCBP population become pregnant whilst taking valproate”, i.e. to assess the effectiveness of the Pregnancy Prevention Programme, rather than examining the outcomes of pregnancy (which are already well established).</li> </ul>
<p>15 March 2018</p>	<p>Sanofi commenced submission of educational materials as recommended by the PRAC, to MHRA for review and approval.</p> <p>Dear Healthcare Professionals Communication (“DHPC”) (doctors and specialists): submitted 20 March 2018; approved 15 June 2018.</p> <p>DHPC (pharmacists): submitted 20 March 2018 approved 15 June 2018.</p> <p>HCP guide: submitted 19 March 2018 approved 10 May 2018.</p> <p>Patient guide: submitted 19 March 2018 approved 10 May 2018.</p> <p>Patient card: submitted 15 March 2018 approved 02 May 2018.</p> <p>Warning label for pharmacy ‘white boxes’: submitted 15 March 2018 approved 20 March 2018.</p> <p>Annual Acknowledgement of Risk Form: submitted 21 March 2018 approved 10 May 2018.</p> <p>Pharmacy Poster: submitted 05 June 2018 approved 15 June 2018.</p> <p>Electronic versions of the Educational Materials and were published on the eMC website during May following MHRA approval and the DHPCs and Pharmacy Poster were added in June once approved.</p>

	Materials were sent for printing to allow hard copy distribution of the packs.
20 March 2018	Sanofi met with MHRA – update on actions since last meeting.
20 March 2018	Sanofi UK submitted applications for variations to the valproate marketing authorisations to implement the outcome of the Article 31 referral in the UK SmPCs. Note this was before the CMDh final decision, at the request of the MHRA. The variation (SmPC was approved on 30 April 2018, with leaflet text. Mock ups were approved during May, with the final approval received 30 May 18. Leaflets to be implemented into production within 3-6 months of approval of individual leaflets.
April 2018	NICE Guidelines were updated in line with the recommendations of the PRAC <sup>45</sup> . The Guidelines are currently undergoing a full review.
18 April 2018	Sanofi submitted applications to add the pregnancy pictogram to the primary packaging of all valproate products (blister). This change was approved on 2 May 2018, to be implemented into production within 6 months of approval.
20 April 2018	Sanofi wrote to the MHRA submitting the PSUR for sodium valproate for the period 24 January 2015 - 23 January 2018. This was a routine submission in respect of the Epilim marketing authorisations.
8 May 2018	Sanofi submitted an application for a variation to the existing marketing authorisations to add a 30s pack size to Epilim and Depakote packs where 30s were not currently registered. This was approved on 14 May 2018. Artwork for cartons was submitted on 30 May 2018 and approved on 8 June 2018.
31 May 2018	The European Commission adopted a final decision following the Article 31 referral, confirming the recommendations of the PRAC in an EU-wide legally binding decision.

<sup>45</sup> NICE Guideline: The epilepsies - The diagnosis and management of the epilepsies in adults and children in primary and secondary care 2004 (Updated 2018) (CG20)



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## Response to Question 10

### Please can you briefly summarise the actions you are taking so you comply with the pregnancy prevention plan?

Sanofi is committed to the safe use of its medicines and to the success of the Valproate Pregnancy Prevention Programme (PPP) – branded *Prevent*.

Sanofi's role is to communicate the Prevent programme to Health Care Professionals (HCPs). HCPs are responsible for compliance with the programme and the new regulatory changes.

The Pregnancy Prevention Programme requires that all women of child-bearing potential prescribed valproate meet the following conditions:

The prescriber must ensure that:

- Individual circumstances are evaluated in each case, involving the patient in the discussion to guarantee her engagement, discussing therapeutic options and confirming her understanding of the risks and the measures needed to minimise those risks.
- The possibility for pregnancy is assessed in all female patients.
- Any female patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- All female patients understand the need and undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- All female patients are counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception [further details are provided] without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
- Every female patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- Every female patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The programme also includes actions for pharmacists, who must:

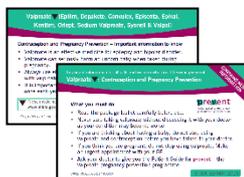
- Ensure the Patient Card is provided every time valproate is dispensed.

- Remind patients of the risks in pregnancy and the need for highly effective contraception.
- Remind patients of the need for annual specialist review.
- Ensure the patient has received the Patient Guide.
- Dispense valproate in the original package. In situations where repackaging cannot be avoided always provide a copy of the package leaflet and add a sticker with the warning to the outer box.
- If a woman of childbearing potential reports that she is not taking highly effective contraception, refer her to her GP (including by contacting the GP if necessary).

While the content of materials informing HCPs of the Prevent programme requires regulatory approval, Sanofi has collaborated closely with the Medicines and Healthcare Products Regulatory Agency (MHRA) to ensure that the information has been appropriately designed and communicated to HCPs, including through the distribution of over 150,000 packs of educational materials to HCPs by post between July and September 2018. Sanofi coordinated this campaign on behalf of all the other companies who are Marketing Authorisation Holders (MAH) for medicinal products containing valproate in the UK.

The *Prevent* materials provide clear guidance for HCPs to follow to ensure compliance with the programme.

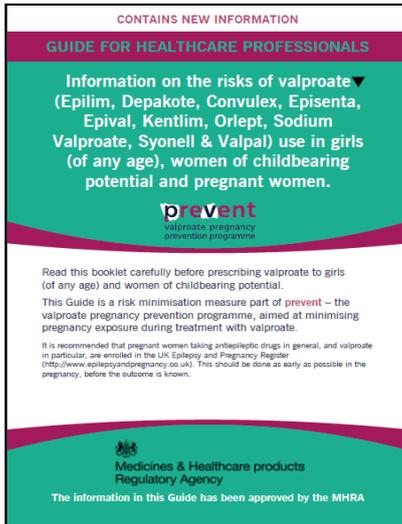
- Patient Cards – to be given by pharmacists to all female patients who are dispensed valproate medicines to remind them of the risks and the actions they must take to minimise exposure during pregnancy.



- Patient Guide – to be provided to women of childbearing potential and girls (of any age) (or their parent/caregiver/responsible person) taking any medicine containing valproate.



- Guide for Healthcare Professionals – for all prescribers, pharmacists, and other healthcare providers involved in the care of girls and women of childbearing potential using valproate medicines.



- Risk Acknowledgement Form – for the specialist and patient (or their parent/caregiver/responsible person) to sign at initiation of any valproate medicine and at treatment reviews at least every year. The patient should receive a copy of the form; one copy should be filed in the specialist notes, and one copy sent to the patient's GP.

VALPROATE RISK ACKNOWLEDGMENT FORM	
To be completed with all girls and women of childbearing potential treated with valproate medicines (sodium valproate [Convulex <sup>®</sup> , Epilim <sup>®</sup> , Episenta <sup>®</sup> , Epival <sup>®</sup> , Kentlim <sup>®</sup> , Orlept <sup>®</sup> , Valpal <sup>®</sup> ], valproic acid, sodium valproate [Epilim <sup>®</sup> ], valproate semisodium [Depakote <sup>®</sup> , Syonell <sup>®</sup> ]).	
This form is for women or girls to read, complete, and sign during a visit with the specialist: when starting treatment, at the annual visit, and when they plan a pregnancy or are pregnant. This is to make sure that women or girls, or their caregiver/legal representative, have discussed with their specialist and understood the risks related to using valproate during pregnancy.	
Name of patient (or their parents/legal guardian or caregiver for children or patients without capacity to make an informed decision): _____ Date: _____	
Name, role, and signature of specialist: _____	
Part A. To be completed and signed by the specialist	
I confirm that the above-named patient needs valproate because:	
• her condition does not respond adequately to other treatments or	<input type="checkbox"/>
• she does not tolerate other treatments.	<input type="checkbox"/>
I confirm that I have discussed the following information with the person named above:	
The overall risks in children exposed to valproate during pregnancy are:	<input type="checkbox"/> Discussed
• an approximately 10% chance of birth defects	
• a 30 to 40% chance of a wide range of early developmental problems that can lead to learning difficulties.	
The conditions of the pregnancy prevention programme (as below) must be fulfilled	<input type="checkbox"/> Discussed
Valproate should not be used during pregnancy (except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments)	<input type="checkbox"/> Discussed
The need for regular (at least annually) review and the need to continue valproate treatment by a specialist	<input type="checkbox"/> Discussed
The need for a negative pregnancy test at treatment initiation and as required thereafter (if childbearing potential)	<input type="checkbox"/> Discussed
The need to arrange an appointment with her specialist as soon as she is planning pregnancy to ensure timely discussion and switching to an alternative treatment before conception and before stopping contraception.	<input type="checkbox"/> Discussed
The need to contact her GP immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.	<input type="checkbox"/> Discussed
The patient or caregiver/legal representative has a copy of the patient guide, and knows that information can also be found online at <a href="http://www.medicines.org.uk">www.medicines.org.uk</a> by entering "valproate" in the search box and then click on "Risk Materials" next to any of the medicines that appear.	<input type="checkbox"/> Discussed
In case of pregnancy, I confirm that:	
• We have discussed options for switching treatment	<input type="checkbox"/>
• She is fully aware of the risks associated with pregnancy; a consent to counselling	<input type="checkbox"/>
The specialist must provide this form to girls and women of childbearing potential treated with valproate (or their caregiver/legal representative), read it themselves and then discuss it with the patient (or her legal representative) to make sure all the risks and information related to the use of valproate during pregnancy are understood. A copy of this completed and signed form shall be kept recorded by the specialist. The practitioner is advised to save an electronic version in the patient dossier. Copies of the completed and signed form should be given to the patient and also sent to their GP.	
This form expires on _____ (date 12 months from now).	

- Pharmacy Poster – for pharmacists to display in the dispensary area to remind pharmacy staff of these requirements.



- Warning stickers for white boxes – for pharmacists to be used if valproate is dispensed out of its original packaging.



As well as collaborating with the MHRA in relation to the drafting, compilation and distribution of the Prevent materials, the measures we have taken include:

- Updating the pop up messages on the dispensing screen used by pharmacists, which we originally introduced in 2017 to prompt pharmacists to remember to communicate the valproate warnings, to include the Prevent programme messaging prompts.
- Reinforcing messaging to all of Sanofi's Epilim and Depakote sales force to prompt and remind HCPs about the changes.

- Implementing more prominent on pack communications for all indications of Epilim and Depakote, as required by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (PRAC). Some images below to illustrate what the on pack communications looks like:

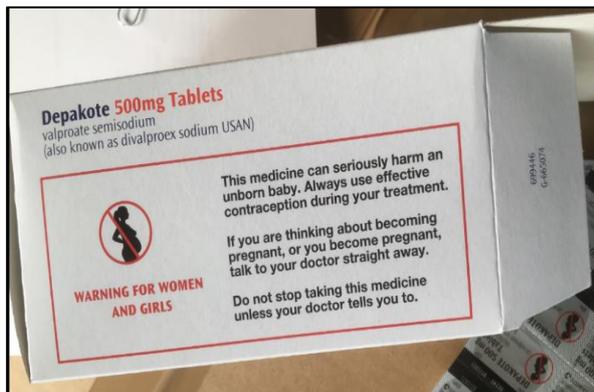
Epilim pack:



Epilim foil:



Depakote pack:



Depakote foil:





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## Response to Questions 11 & 12

Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated.

Please describe the steps you take in your post-marketing vigilance, and any policies you've introduced to recognise and respond to events proactively.

Sanofi is committed to ensuring that its medicines are used as safely as possible and follows EU pharmacovigilance requirements and associated regulatory guidance as summarised in the response to Q13.

Sanofi internal policies/processes ensure currently available information relevant to the benefit-risk profile of its medicines is made available to the regulatory authorities (in the UK, the MHRA), healthcare professionals (HCPs) and patients in the form of individual /aggregate safety reports, Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) respectively.

Strict rules apply to all products under Sanofi's responsibility. The key steps employed by the company for its pharmacovigilance activities are the collection and data processing of all reported safety information, the review of single case and aggregate data assessment for safety signals, the categorisation and management of product risk, the communication of risks and the monitoring of any risk minimisation actions taken. Sanofi's pharmacovigilance system is regularly inspected by regulatory authorities, including the European Medicines Agency (EMA) and the MHRA.

The different steps of safety signal detection and surveillance as defined by current company procedures are described in the response to Q13 and summarised below:

### Organisation

1. Sanofi safety signal management process involves continuous monitoring of the safety profile of each product, including valproate, using appropriate tools (external and internal pharmacovigilance databases) and communication of these elements to the regulatory authorities.

### Detection sources

2. Sources of information, including spontaneous reports of individual cases, scientific literature and solicited reports from organised data collection systems are regularly and proactively screened by both regulatory authorities and the MAH to identify any signals to ensure that appropriate action is taken in response to new evidence which may impact the known risk-benefit balance.

### Detection methods

3. Signal detection activities involve two complementary approaches through a combination of qualitative and quantitative signal detection methods.

### Signal and Risk Management

4. When a signal is identified, the possibility of a causal association is evaluated through assessment of all relevant safety data. Within Sanofi, such data are reviewed within a designated safety governance committee. Any safety signal which is detected is processed as per Sanofi SOP "Safety Signal and Risk Management" and captured in a safety information tracking system.



5. Safety signals that have been detected following the qualitative or quantitative review of safety data are assessed by the Safety Governance Committees involving transversal competencies (legal, medical, regulatory affairs) detailed as per Sanofi SOP "Global Pharmacovigilance and Epidemiology Safety Governance".

#### **Communication with regulatory authorities**

6. Regulatory authorities are promptly informed of Sanofi's assessments, where relevant, at any stage of the signal management process and ICSRs are reported daily through Eudravigilance system. The regulatory authorities independently review the assessments submitted by MAHs, including Sanofi, and arrive at their own conclusions in relation to benefit-risk.

#### **Dissemination to Patients, Carers and Healthcare Professionals**

7. When a risk is identified, Sanofi liaises with the regulatory authorities and suggests an update of the product information (SmPCs and PILs). This may only be revised with the approval of the competent regulatory authority which, in the case of Epilim and Depakote supplied in the UK, is the MHRA.
8. Sanofi has always reported cases involving use of valproate during pregnancy to the competent regulatory authorities. The safety profile of valproate is routinely updated and documented in the local product information according to the available scientific knowledge.
9. A range of other methods are used to disseminate information to patients, carers and HCPs and reinforce the content of the product information. These methods are described in the response to Q13.



## Response to Question 13

### In your view, where within the healthcare system does your responsibility as a manufacturer for disseminating and responding to adverse event reporting begin and end?

#### Investigation and reporting of adverse drug reactions

1. Since at least 1971, pharmaceutical companies in the UK have been obliged to report adverse drug reactions (“ADRs”) to the regulatory authorities (SI 1971/972). Standard Directions issued by the Department of Health required any company holding a product licence for a medicinal product to report adverse effects associated with use of the product and originating from the UK as soon as possible after receipt or, where appropriate, immediately after substantiation by the patient’s doctor. This requirement applied to any report made or confirmed by a medical or dental practitioner, a pharmacist, coroner or procurator fiscal and which related to an adverse effect which had occurred at doses in normal use, could impact the assessment of benefit risk and fell within one of the following categories:
  - (a) A reaction with a fatal outcome;
  - (b) A reaction of sufficient severity to interfere with normal activities;
  - (c) Any unusual reaction, not referred to in standard publication or in literature issued by the manufacturer or licence holder; or
  - (d) Any reaction which may be an example of a possible drug interaction.

The licence holder was also required to provide information to the regulatory authorities about suspected adverse reactions from abroad “without delay” if these suggested “an associated serious hazard”.

2. From 1971, pharmacovigilance obligations have become consistently more extensive and sophisticated. While the following details are not intended to be comprehensive, they are provided to illustrate the development of pharmacovigilance requirements applicable in the UK:
  - (a) From 1984, serious reactions (defined as those which are fatal, life-threatening, disabling or incapacitating and expressly including congenital malformations) originating in the UK were to be reported immediately; reports also had to be made in relation to minor effects originating from the UK relating to new products and effects from abroad which were both serious and unpredictable (i.e. not listed in the data sheet or scientific literature).
  - (b) From 1987, serious adverse reactions occurring in phase IV trials were required to be reported immediately with minor effects reported by way of a summary at the conclusion of the trial; adverse effects described in published scientific literature also had to be reported.
  - (c) Directive 93/39/EEC, revised pharmacovigilance obligations by:
    - Introducing the requirement for the person responsible for placing a medicinal product on the market (subsequently revised to refer to the marketing authorisation holder (“MAH”)) to have permanently and continuously at their disposal a qualified person for pharmacovigilance, who is responsible for establishing and maintaining a system which ensures that information about all suspected adverse reactions are collected at a single point within the EU and reported to the regulatory authorities and for

responding to requests from the regulatory authorities for information necessary for the evaluation of the risks and benefits of the product.

- Stating that all suspected serious ADRs reported by a healthcare professional were to be followed up and reported to the competent regulatory authorities within 15 days and all other suspected ADRs reported by a healthcare professional were to be reported on request or at least every 6 months within the first 2 years, once a year for the following 3 years and thereafter every 5 years, accompanied by a scientific evaluation (so called “periodic safety update reports” (“PSURs”)).
  - (d) The UK competent authority (at that time the Medicines Control Agency (MCA)) issued guidance in March/April 1997 on reporting adverse reactions arising from prospective pregnancy registries, confirming that serious suspected adverse reactions from such registries were subject to 15 day expedited reporting and stating that reports should not be made before the outcome of the pregnancy was known and that individual adverse outcomes should not be reported unless they were suspected by a healthcare professional to be drug related. Non-serious suspected adverse reactions from pregnancy registries were to be reported within PSURs, as were all normal outcomes.
  - (e) EU guidance on pharmacovigilance (Volume 9 of Notice to Applicants) was published in 1999 (previously guidance had been available in draft form). The guidance included specific requirements for reporting outcomes of use during pregnancy. The guidance was updated in 2001 and 2004
  - (f) Directive 2000/38/EC made various changes to existing pharmacovigilance obligations including revising the definitions for “adverse reaction”, “serious adverse reaction” (to include expressly all congenital anomalies or birth defects) and “unexpected adverse reaction”.
  - (g) Directive 2001/83/EC consolidated existing EU obligations.
  - (h) Directive 2004/27/EC amended Directive 2001/83/EC, including through the following pharmacovigilance requirements:
    - The MAH was required to record and report all suspected serious adverse drug reactions notified by a healthcare professional and all other suspected serious drug reactions which met the notification criteria to the regulatory authorities in the territory where such reaction occurred.
    - Suspected serious unexpected adverse drug reactions occurring in the territory of a third country also had to be reported.
    - The timelines for submission of PSURs were revised
    - In 2005, the European Commission commenced a review of European systems of safety monitoring and, following a period of public consultation, this resulted in the adoption of Directive 2010/84/EU and Regulation (EU) No 1235/2010, accompanied by Commission Implementing Regulation No 520/2012.
    - Further amendments were made by Regulation (EU) No 1027/2012 and Directive 2012/26/EU and have been clarified in subsequent guidance issued by the EMA and Heads of Medicines Agencies.
3. The obligations mentioned above are placed on MAHs and not manufacturers. Sanofi has complied with its pharmacovigilance obligations as these have developed over time.

### **Pharmacovigilance System**

4. Sanofi’s pharmacovigilance obligations are currently comprised of a pharmacovigilance system

operated in parallel with the regulatory authorities (in the UK, the MHRA). For nationally authorised medicinal products, such as Epilim and Depakote, this now includes the activities listed below.

5. The collation and documentation of individual case safety reports of suspected adverse reactions (ICSR), from various sources

- (a) Spontaneous reports received from both healthcare professionals and consumers, including those reported in the press, communicated by patient organisations to their members, obtained from social or digital media under the management or responsibility of the MAH, collected from non-interventional post-authorisation studies where the protocol does not require their collection and from named patient use.
- (b) Systematic literature review, conducted at least weekly, of widely used reference databases and local journals
- (c) Solicited reports from organised data collection systems which include clinical trials, non-interventional studies, registries, post approval named patient programmes, other patient support and disease management programmes, surveys of patients of healthcare professionals and other types of proactive information gathering.

The MAH organizes the follow-up of cases in order to obtain all the required information for a thorough medical assessment of the cases and evaluation of the causal relationship between the reported reaction(s) and the suspect medicinal product. For instance, the MAH would collect the outcomes of all pregnancies where the embryo or foetus may have been exposed to the medicinal product.

The analysis of ADRs by a MAH is constrained by the number of ADRs which are actually reported, and the details of information provided by HCPs in relation to each ADR. In the UK, while HCPs are encouraged to report suspected ADRs and to assist in the investigation of these, there is no legal obligation for them to do so. Furthermore, all investigation and reporting of ADRs is conducted in the context of data privacy requirements and the need to protect patient confidentiality.

6. Reporting to regulatory authorities

(a) **ICSR reporting:**

- (i) All suspected serious ADRs, defined as any response to a medicinal product which is noxious and unintended, that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly/ birth defect, that occur in the Union and in third countries must be reported to the Eudravigilance database (EMA database) within 15 days following the day on which the MAH concerned gained knowledge of the event.
- (ii) MAHs also submit all non-serious suspected ADR reports that occur in the Union, within 90 days following the day on which the MAH concerned gained knowledge of the event.

- (b) **Periodic Safety Reports:** the main objective of a Periodic Safety Update Report (PSUR) also called Periodic Benefit Risk Evaluation Report (PBRER) is to present to regulatory authorities a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The PSUR should be submitted to regulatory authorities immediately upon request; at least every six months after a

marketing authorisation has been granted and for the first two years following the initial placing on the market; once a year for the following two years; and thereafter at three-yearly intervals. It will contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

- (i) examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile;
- (ii) summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- (iii) summarising any important new efficacy/effectiveness information that has become available during the reporting interval; and
- (iv) where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

7. Signal detection and assessment

- (a) Sources of information including individual case safety reports reported globally, scientific literature and solicited reports from organised data collection systems, are regularly and proactively screened by both regulatory authorities and the MAH to identify any signals to ensure that appropriate action is taken in response to new evidence which may impact the known risk-benefit balance.
- (b) When a signal is identified and validated for further assessment, the possibility of a relationship between the treatment and the event is then evaluated through analysis of all available relevant safety data including aggregate data compiling relevant case safety reports related to the topic being assessed, scientific publications and non-clinical data, where relevant.
- (c) At Sanofi, these data are presented for adjudication to a safety governance committee which assesses whether the cumulative weight of evidence reasonably supports a relationship between the relevant medicinal product and the signal. The committee will also consider whether the signal constitutes an important potential or identified risk.
- (d) If a risk is identified, a benefit-risk evaluation is carried out proactively by the MAH and independently by the regulatory authority. The regulatory authority is ultimately responsible for determining whether benefits continue to outweigh risks and, for important risks, whether measures should be put in place to improve the benefit-risk balance through risk minimisation activities (e.g., labelling changes, communications with prescribers, or other steps) and how information on the newly identified risks should be disseminated.

8. Dissemination to patients, carers and healthcare professionals

- (a) The principal means of communicating information to patients, carers and healthcare professionals is through the product information (SmPCs and PILs) as regularly updated to reflect developing experience on use of the product. The content of both SmPCs and PILs must be approved by the regulatory authorities as accurately reflecting the current state of scientific and medical knowledge, before it is put into circulation. Sanofi routinely publishes all SmPCs, PILs, DHPCs and Educational Materials on the Electronic Medicines Compendium (eMC).
- (b) However communication channels have become more numerous and varied over time as developments in technology and legislation have extended the channels available.

- (i) Direct healthcare professional communications (DHPCs) are communications by which important safety information is provided directly to individual HCPs by a MAH or competent regulatory authority to inform them of the need to take specific action or to adapt their practices to a medicinal product. The regulatory authority may disseminate or request the MAH to disseminate a DHPC in any situation where the regulatory authority considers this to be necessary for the safe and effective use of the medicinal product. DHPCs require co-operation between the MAH and the regulatory authority and agreement in relation to the content, intended recipients, timetable and channels of communication is required before a MAH may issue a DHPC. For example, Sanofi has disseminated DHPCs following EMA's Pharmacovigilance Risk Assessment Committee (PRAC) referrals on valproate containing products in February 2016, May 2017 and June-September 2018. Additionally, in January 2015, the MHRA issued a DHPC via the Central Alerting System (CAS) to inform HCPs of the outcome of the PRAC referral on valproate that had reported in November 2014.
- (ii) Educational materials, such as patient or HCP guides, may be developed and disseminated by regulatory authorities or by MAHs, after the validation and approval of the regulatory authorities. Such materials may be distributed directly to HCPs and/or patients or may be posted on websites of the regulatory authorities or the MAHs. Examples of such materials are the guidance issued by MHRA in relation to the valproate pregnancy prevention programme which was published by MHRA on its website and also by Sanofi; and the Patient Booklet and Patient Card that have been developed for valproate containing products following the recent PRAC review.
- (iii) Responses to requests by individual HCPs for information may be provided by regulatory authorities and MAHs.
- (iv) Both regulatory authorities and MAHs may issue press releases and press briefings to journalists referring to the regulatory action taken by the competent authority. For example, MHRA published a Press Release on 24 April 2018 stating that *"Valproate [was] banned without the pregnancy prevention programme"*.
- (v) Competent regulatory authorities and MAHs may have systems in place for responding to enquiries about medicines from individual members of the public. Guidance issued by the EMA and the Heads of Medicines Agencies states that such responses should take into account information which is in the public domain and should include the relevant recommendations to patients and health care professionals issued by competent authorities. Where questions relate to advice on individual treatment, patients should be advised to contact a health care professional.

## 9. Risk Minimisation Activities

- (a) A European Medicines Agency (EMA) review in 2014 (Referral Article 31 procedure EMEA/H/A-31/1387) resulted in amendments to the product information for valproate products, including strengthening of the wording to reflect the current knowledge of risks of developmental disorders and congenital anomalies and communication to healthcare professionals through a DHPC. In addition, educational materials were put in place in order to ensure that healthcare professionals and patients were informed about the risks associated with valproate in pregnant women and women of childbearing potential and on the measures necessary to minimise the risk. The Educational Materials stipulated by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) included a Guide for HCPs, a Patient Guide and a Checklist outlining risks of valproate use during pregnancy to be completed by Specialists at least annually.

- (b) Additionally in the UK, a Patient Card, and a boxed warning on the product cartons was agreed with MHRA during 2016.
- (c) A drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate was also put in place and to assess the effectiveness of the measures put in place following the referral (2013/2014).
- (d) In March 2017, the French medicines regulatory authority, ANSM, initiated a further referral under Article 31 of Directive 2001/83/EC, in view of evidence from France that, despite the measures that had been put in place, prescribers had not followed prescribing requirements and prescribing patterns had not been sufficiently altered. Following further consideration by the PRAC, new regulatory measures, were approved by the European Commission in May 2018. These measures are described in responses to Q9 and Q10.
- (e) Risk management plans (RMPs) are a recent development and are now required for all applications for a new marketing authorisation and may be introduced for some older medicinal products. The nature of such RMPs will depend on the particular product and any related safety concerns.

10. Collaboration in risk minimisation activities

Sanofi has at all times worked closely with regulatory authorities and HCPs to share developing knowledge about risks associated with valproate products and to support safe use of such products where these are clinically appropriate for the treatment of patients.

However, although the MAH plays a role in disseminating new safety information through product information update and risk minimisation activities, it is to be emphasised that the effectiveness of risk minimisation activities requires the collaboration of every player in the healthcare chain that cares for the patients concerned. The MAH is not permitted to interact directly with patients and may not provide advice regarding personal medical matters. So, while the MAH (in collaboration with the regulatory authority) provides the measures e.g. educational materials, it is the responsibility of HCPs to prescribe appropriately in the context of the individual patient, their medical condition and personal circumstances, to consider switching treatment consistent with recommendations in the SmPC and authoritative guidance, to carry out relevant investigations where needed before prescribing (including pregnancy testing) and to communicate information and advice regarding risks to patients, including counselling on use of valproate by women and girls of child-bearing potential.



Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence. Reference: AZNFVK. Oct 18

## Response to Question 14

**Who has the final say on what should be included on the data sheets and patient information leaflets? If you have exceeded the minimum requirements specified by the regulator please provide details.**

### **The UK competent regulatory authority for Sanofi's sodium valproate medicinal products**

1. The UK competent regulatory authority responsible for the oversight of medicinal products authorised nationally was, prior to 1989, the Department of Health Medicines Division; in 1989, the Medicines Control Agency ("MCA") was established and, in 2003, the MCA merged with the Medical Devices Agency ("MDA") to form the Medicines and Healthcare products Regulatory Agency ("MHRA"). These have been the regulatory bodies responsible for the supervision of Sanofi's valproate products in the UK.

### **Data sheets / Summaries of Product Characteristics (SmPCs)**

2. Pharmaceutical companies in the UK have, at all material times, provided information relating to medicinal products to healthcare professionals in the form of data sheets or summaries of product characteristics ("SmPCs").
3. The form and content of datasheets were set out in the Medicines (Data Sheet) (Transitional) Regulations 1971 and, subsequently, the Medicines (Datasheet) Regulations 1972. Datasheets were required to include the prescribed information and only the prescribed information and to be consistent with the product licence for the medicinal product, but were otherwise the responsibility of the manufacturer.
4. SmPCs were introduced by Directive 83/570/EEC, which amended Directive 65/65/EEC (the original legislation that harmonised regulation of medicinal products in the European Economic Community). Directive 83/570/EEC introduced a requirement for manufacturers to submit a draft SmPC with an application for a product licence and specified the categories of information which were to be included. The current requirements in this respect are now set out in Article 11 of Directive 2001/83/EC, implemented in the UK by Part II of Schedule 8 to the Human Medicines Regulations 2012. Additional or different categories of information are not permitted. SmPCs were required for both applications for new marketing authorisations (which replaced product licences) and applications for renewals, from 1995.
5. The SmPC forms an integral part of the marketing authorisation for a medicinal product. It is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. .
6. As explained above, the manufacturer is required to include a proposed SmPC, including the specified categories of information, in its application for a marketing authorisation. This proposal is then reviewed and, if necessary, revised by the competent regulatory authority during the assessment of the application. When a marketing authorisation is granted, the marketing authorisation holder is informed by the competent authority of the SmPC which has been approved and this sets out the agreed position of the medicinal product as distilled during the assessment process.
7. The marketing authorisation holder may not make any change to the SmPC without the approval of the regulatory authority. The marketing authorisation holder may propose amendment of existing SmPCs by making an application for a variation of the marketing authorisation and this

application may be accepted, rejected or revised by the regulatory authority after considering the proposed changes in the context, where appropriate, of the current medical and scientific data for that product. Alternatively, the regulatory authority may impose a change to the SmPC in response to developing knowledge of the product obtained, for example, through clinical trial data, published literature or pharmacovigilance activities.

8. Sanofi has regularly applied to vary the marketing authorisations for its valproate products in order to amend the associated SmPCs, consistent with the developing scientific and medical evidence regarding the product. While the data relating to use of valproate in pregnancy has generally been difficult to interpret, Sanofi has adopted a precautionary approach, liaising with the regulatory authority and proposing warnings be added to the SmPCs when the available data raised a reasonable suspicion of a potential adverse reaction, even where the evidence fell short of establishing a causal relationship.
9. The contents of SmPCs are not characterised as minimum requirements, which may be exceeded by the marketing authorisation holder. As explained above, the categories of information to be included in an SmPC are defined in legislation and the content is approved by the regulatory authority. No amendment or addition to the approved content is permitted without a further application for a variation to the marketing authorisation. Such variation will be approved only if it is considered by the regulatory authority to be appropriate and supported by data.

#### **Patient Information Leaflets (PILs)**

10. Prior to Directive 92/27/EC, there was no legal obligation to provide patient information leaflets with medicinal products. Such patient information leaflets could be supplied on a voluntary basis. Where a product licence holder elected to provide a PIL, it had to comply with the Medicines (Leaflets) Regulations 1977 (SI 1977/1055), which specified the information to be included in a PIL (where supplied) and included a requirement that product licence holders should submit any proposed PILs to the regulatory authority for approval prior to putting them into circulation.
11. In 1984, the Association of the British Pharmaceutical Industry (ABPI) set up a Working Party to produce a report on the provision of information to patients in relation to their medicines. The Working Party consulted with 34 interested organisations including Royal Medical Colleges, the National Consumer Council, the Consumer Association and the Patients Association. An interim report was issued as a consultation document in February 1987. The overall conclusion of the Working Party was that information should be provided to patients with their medicines, to reinforce and amplify that which may already have been given by the doctor or the pharmacist, although it was recognised that such an approach was potentially complicated. With respect to the content of information provided to patients, the consensus of the consultation was that information should be brief and concise: “the emphasis must be to reinforce and not replace information given by the doctor or pharmacist”. There was considerable debate about the level of detail that should be provided and many doctors were concerned that the provision of too much information would act as a deterrent to patients and that detailed information on side effects was not in their best interests. With respect to pregnancy, the Working Party Report concluded that the contents of a PIL should include “advice to inform doctor if pregnant”. Sanofi was strongly supportive of this initiative by ABPI and was concerned to introduce PILs for Sanofi’s products when guidelines were published.
12. In March 1988, following further consultation, the ABPI issued a Guideline entitled “Patient Information; Advice on the Drafting of Leaflets” recommending the provision of PILs in order to supplement advice given by doctors and pharmacists. The Guideline, which was based on research conducted by Professor Charles George at Southampton University, stated that “the prime reason for providing information leaflets was to improve patient understanding of the use of their

medicines” and recommended that leaflets should be “succinct and intelligible”. The Guideline listed the information to be included in a leaflet, with the emphasis on a simple summary of relevant information; a sample PIL for a fictitious product “Bloggofen” was attached. The ABPI “highly recommended” compliance with it.

13. The first PIL for Epilim was introduced in 1989. There was considerable discussion about the wording and how the information provided to patients should be phrased. Sanofi was particularly concerned regarding the wording of the pregnancy warnings; the company wanted appropriately to reflect the limited indication for use of the product in women of child-bearing age and to encourage them to discuss treatment with their doctors, but not to cause them to discontinue necessary treatment without appropriate medical advice. The 1989 PIL closely followed the ABPI Guidelines and the Bloggofen precedent leaflet. It advised patients to read the leaflet before commencing treatment with Epilim, stating: “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”. In addition to this overarching statement, the PIL contained three separate statements regarding pregnancy, aimed at women of child-bearing age, reflecting the Company’s wish to ensure that any patient who continued to take Epilim during pregnancy only did so after proper discussion with their treating doctor about the potential risks and benefits of such treatment in the context of their particular medical condition and circumstances.
14. New European legislation (Directive 92/27/EC (implemented in the UK by the Medicines (Leaflets) Amendment Regulations 1992) introduced substantial changes in the regulatory requirements for patient information and was mandatory for all new licences granted and all licence renewals after 31 December 1993.
15. As a result of the new legislation, the form and content of PILs were harmonised throughout the EU. The Directive resulted in a substantial increase in the quantity of information provided by manufacturers to patients and set out detailed provisions as to the type of information and the sequence in which it should be included. The legislation made provision for the inclusion of “specific warnings” including those which “take into account the particular condition of certain categories of users” (including pregnant or breastfeeding women). The new requirements were controversial and many doctors still believed that the provision of detailed generic information to patients (i.e. information that was not tailored to their particular circumstances) could be confusing and even harmful and that it could undermine the doctor-patient relationship.
16. In summary therefore, the form and content of PILs, as with SmPCs, are governed by legislation and must be approved by the regulatory authority before they can be included in packs of medicinal products. A draft PIL, based on the SmPC, is submitted to the regulatory authority as part of the application for a marketing authorisation and the applicant is subsequently notified of the final approved version when a marketing authorisation is granted. Any subsequent amendment of the PIL must either be proposed by the marketing authorisation holder, submitted to the regulatory authority who may revise this as it considers appropriate, before it is approved or, alternatively may be imposed by the regulatory authority. In any case however no PIL can be put into circulation before it has received regulatory approval.
17. The information included in the PILs provided by Sanofi in relation to their valproate products has been updated in line with the SmPCs to reflect the developing scientific literature as this has evolved over time and have at all times been approved by the regulatory authority, which has closely monitored sodium valproate’s safety profile.
18. As with SmPCs, there is no minimum requirement for PILs imposed by the regulatory authority. The categories of information which must be included in a PIL are defined by legislation and additional categories are not permitted. The content of any PIL must be approved by the

regulatory authority before it is put into circulation, as must any addition or amendment to it.

19. Finally, PILs accompanying prescription only medicines, such as those containing valproate, are intended to supplement, but not replace, the advice of the prescribing doctor, who is able to direct the available scientific and medical information, including that in the SmPC, to the medical condition and particular circumstances of the individual patient.

#### **Additional initiatives**

20. Sanofi has been involved in a number of initiatives beyond provision of the datasheet/ SmPC and PIL, to increase knowledge, understanding and awareness among healthcare professionals (including pharmacists) and patients, of the risks associated with the use of valproate in pregnancy. All such information reflected the content of the data sheet / SmPC consistent with regulatory requirements. The number of these initiatives are too many to list individually, however some examples conducted during the period while Epilim has been available in the UK are provided below.

#### Conferences, seminars and medical education

21. Since the early 1980s, Sanofi has regularly organised post-graduate educational meetings and symposia to facilitate discussion between epilepsy experts regarding the use and effects of sodium valproate.
22. In 1983 and 1989, Sanofi sponsored international symposia on epilepsy and sodium valproate, which included presentations by epilepsy experts on the treatment of epilepsy in pregnancy. In addition to these symposia, international conferences were also sponsored by affiliated companies and attended by UK healthcare professionals.
23. In 2003, in conjunction with the National Society for Epilepsy, Sanofi produced an educational video, "Seminar on Seizures", addressing some of the challenges faced by those suffering from epilepsy, and including presentations by eminent clinicians in the field. It was aimed at GPs and other healthcare professionals.
24. Currently, Sanofi Medical Advisors are engaged with healthcare professionals via conferences and seminars to help explain the new risk minimisation requirements and to reinforce the advice in the Pregnancy Prevention Programme.
25. Sanofi has also developed a video for use with healthcare professionals concerning implementation of the new PRAC recommendations. This is currently undergoing MHRA review. Sanofi believe that this video will make a useful educational contribution in this area.
26. On a day to day basis Sanofi representatives actively communicate the risks associated with the use of valproate women of childbearing potential to healthcare professionals and this is prominently mentioned in all materials they distribute. Since the recent European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) outcome, Sanofi have updated all materials with information on the PREVENT Pregnancy Prevention Programme (PPP) to increase understanding of what is required and to raise awareness of the PPP.

#### Epilim in Pregnancy Pack

27. During the 1980s and 1990s, Sanofi prepared information to be provided to healthcare professionals who directed queries in relation to certain issues towards the Company (including the "Epilim in Pregnancy pack" which was provided to healthcare professionals who raised enquiries regarding use of sodium valproate in pregnant women or women who might become pregnant). Sanofi would provide any doctor or pharmacist who enquired about use in pregnancy with an information pack, including information on cases of congenital abnormalities reported to the Company, a summary of the available evidence regarding the potential effects of sodium

valproate on the developing foetus from the scientific literature (in some cases, copies of relevant scientific papers would be provided) and a current data sheet. The pack would also include a form for reporting the outcome of pregnancies in women prescribed sodium valproate, on the basis that any enquiry from a doctor or pharmacist was likely to have been prompted by a particular patient who was pregnant or was planning to become pregnant. The information pack was revised frequently to reflect events reported to the Company and developments in the scientific literature.

#### Technical Brochures

28. The company has also produced more general Technical Brochures (which included information regarding valproate, including the risks associated with use in pregnancy) as reference documents for doctors and pharmacists. These were distributed widely throughout the 1980s and 1990s, in response to enquiries by healthcare professionals, but were also provided proactively to neurologists treating patients with epilepsy, drug information departments in hospitals and hospital pharmacists.

#### Pharmacy Initiatives

29. During 2015/2016, Sanofi worked with MHRA to develop the first version of the Patient Card (a card reinforcing warnings about use of valproate in pregnancy to be distributed by pharmacists and discussed at the time every prescription for valproate is dispensed to a woman or girl of childbearing potential), which was introduced in the UK before it became a regulatory requirement.
30. Sanofi has also produced posters and shelf edge materials for use in pharmacies as a reminder of the risks of valproate when used in women of childbearing potential.
31. Additionally, Sanofi funded and implemented a pop-up alert for NHS IT dispensing systems for pharmacists when dispensing valproate for women of childbearing potential, to alert women of the risks and to advise them to contact their doctor if they were not aware. This pop-up alert system is now being expanded by NHS Digital to be included on GP prescribing systems.
32. Sanofi has responded to information provided by patients at the PRAC Valproate Public Hearing last year, that in some cases packs of Epilim are split at pharmacy level with the result that patients receive their medication in white boxes, which do not carry the approved warnings and product information. The Company is reducing the pack sizes of Epilim preparations from 100 tablet packs to 30 tablet packs to ensure that women are dispensed full packs of medicine with the correct labelling, including the pack warning and pictogram. In the interim period, Sanofi has produced stickers for pharmacists to use if they do dispense in white boxes, which contain the pack warning and pictogram.
33. Sanofi believes that the pharmacist has a key role to play in helping to raise awareness of the risks and in implementing the PPP in the UK. As a result Sanofi is currently working to develop an engagement programme with pharmacists to understand how they can facilitate the pharmacy profession in providing the required information to patients and in the implementation of the pregnancy prevention plan.

#### Response to specific enquiries

34. Where a healthcare professional wrote to the Company with a query in relation to a specific issue regarding the use of valproate (including use in pregnancy), either the Medical Information Department or a Company physician would provide a response tailored to the particular enquiry.

#### Information provided to patients

35. The ability of pharmaceutical companies to provide information directly to patients has at all

times been limited by regulatory restrictions and the fact that it is inappropriate for companies to advise patients without knowledge of their particular medical conditions or circumstances. Those concerns are magnified in the context of a serious and complex medical condition such as epilepsy. It is also necessary to take into account the fact that the provision of patient information by pharmaceutical companies was, prior to the requirements under Directive 92/27/EC, viewed as controversial and potentially undesirable.

36. Nevertheless, Sanofi has at all times sought to support the provision of information to patients to increase their knowledge regarding issues associated with epilepsy generally. By way of example:
- (a) The company established the Sanofi Winthrop Epilepsy Support Service to prepare educational materials for patients. Some of this information would have been provided directly to patients who wrote to the Company requesting information regarding their condition. Sanofi would also distribute such material via healthcare professionals or through patient associations such as the British Epilepsy Association (“BEA”).
  - (b) Sanofi also sponsored various guides written by leading clinicians, although the company did not influence the content of the booklet. One of these booklets, entitled “Women and Epilepsy” and distributed in the 1990s, was written by Dr Fiona Fairlie, a consultant obstetrician and gynaecologist and Carina Mack, an epilepsy nurse specialist; the booklet was endorsed by the BEA. The booklet did not include any product specific information but did address the potential effect of epilepsy on pregnancy. One of the issues covered in this section was the risk of foetal abnormality and the booklet advised that such risk could be minimised by pre-pregnancy assessment of medication and, possibly, by use of folic acid supplements. Screening was recommended.

#### Conclusion

37. In summary, Sanofi has at all material times sought to ensure that information and warnings regarding the use of valproate in women of childbearing potential was appropriately discussed and disseminated consistent with available scientific and medical knowledge and the current data sheet / SmPC. A wide range of initiatives were employed to support patients and healthcare professionals in considering these difficult issues and the activities listed above comprise some examples of these.



Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence. Reference: AZNFVK. Oct 18

## Response to Question 15

**Please can you describe the elements of your corporate social responsibility policy which relate to the availability of products, and the risk-benefit analysis for products that you manufacture**

### Availability of products

Article 81 of Directive 2001/83/EC requires that the marketing authorisation holder (“MAH”) of a medicinal product “shall, within the limits of [its responsibility], ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered”.

Sanofi takes this obligation very seriously and is committed to making every effort to ensure that the supply chain will continue to deliver medicines and vaccines to the market without interruption, with the goal of protecting patients’ health every day. As part of this mission, Sanofi endeavours to ensure that:

- There is no interruption of programmes to develop new medicines;
- The monitoring of adverse reactions (pharmacovigilance) is uninterrupted;
- The continuity of our business activity is safeguarded and protected;
- The continuity of activity for the company’s employees is ensured; and
- The continuity of products in the supply chain is also ensured.

### Risk-benefit assessment

The determination of risk-benefit is the key conclusion reached by regulatory authorities in the context of the application for a marketing authorisation (“MA”) for a medicinal product.

Following grant of MA, the MAH keeps the risk-benefit of the product under constant review, together with the competent regulatory authorities throughout the subsequent life of the product, in the context of pharmacovigilance activities. The assessments prepared by the MAH are routinely provided to the regulatory authorities in Periodic Safety Update Reports (PSURs) and at additional times where necessary. These assessments are subject to the approval of the regulatory authority who reviews and updates its conclusions regarding the risk-benefit of the medicinal product.

Sanofi has always complied with its regulatory obligations in terms of submission of risk-benefit assessments for its valproate products to the MHRA. No medicinal product is supplied by Sanofi unless the risk-benefit assessment when used in the approved indication and in accordance with the product information, has been determined to be positive by the regulatory authorities.



Sanofi submission to Independent Medicines & Medical Devices Safety Review Call for Evidence. Reference: AZNFVK. Oct 18

## Response to Question 16

**If applicable, please can you provide a brief summary of litigation and/or settlements relevant to your product(s), both within the UK and worldwide?**

### UK LITIGATION

#### The Foetal Anticonvulsant (FAC) Litigation

1. Between 2003 and 2008, claims were brought against Sanofi-Synthelabo Limited (“SSL”) on behalf of children who alleged that they had suffered various congenital abnormalities as a result of their in utero exposure to sodium valproate (Epilim) taken by their mothers during pregnancy as treatment for epilepsy. Approximately a third of the Claimants were also exposed to other anti-epileptic drugs (“AEDs”) in utero. All the Claimants were funded by the Legal Services Commission.
2. All claims were managed in the High Court in London under the umbrella of a group litigation order (“GLO”) called the “FAC Litigation”.
3. The first claim was served in August 2003, and the first case management hearing took place in March 2005. In June 2006 a moratorium was imposed because legal aid had been withdrawn from the Claimants. The moratorium remained in place until May 2007, when the claimants successfully challenged the withdrawal of legal aid funding by way of judicial review, and legal aid was restored. A cut-off date (29 February 2008) was subsequently imposed by the Court, by which time all Claimants wishing to join the group litigation had to have issued and served a Claim Form, Particulars of Claim and a medical report. Claims that did not satisfy these conditions were stayed, pending the outcome of the FAC Litigation trial. As at June 2009, there were 100 claims in the FAC Litigation, and 36 stayed claims.

#### Alleged Injuries

4. The Claimants alleged that they suffered from a range of injuries which they described collectively as “Foetal Valproate Syndrome” (a very small number of cases alleged the more generic “Foetal Anticonvulsant Syndrome”). Almost all of the Claimants alleged facial dysmorphism and some form of neurodevelopmental delay/autism/behavioural problems. A range of other injuries were also alleged in some cases, including: neural tube defects, heart defects, skeletal abnormalities and limb defects, cleft lip/palate, urogenital defects, contracture deformities, hypotonia (decreased muscle tone), walking problems, glue ear and myopia.

#### Legal basis of the claims

5. The claims were all brought under the Consumer Protection Act 1987 (“CPA”), which implemented the Product Liability Directive 85/374/EEC (“the Directive”) in the UK, and the Congenital Abnormalities (Civil Liability) Act 1976 (“CDCLA”). The Claimants alleged that Epilim was a defective product under the CPA in that it was not as safe as persons generally were entitled to expect. They defined the defect as the “teratogenic capacity” of the drug and their primary case was that little weight should be given to the warnings supplied with the product in Patient Information Leaflets (PILs), which, they said, could not save the product from a finding of defect. However, in the alternative, they claimed that the warnings provided by SSL were inadequate.
6. It was common ground that Epilim was efficacious, life saving and required for the medical treatment

of a serious condition. The Claimants stated that taking sodium valproate placed an epileptic woman of childbearing potential in an “impossible dilemma” because of the need to take the drug to reduce the risk to herself and her putative foetus because of her epilepsy on the one hand, and the risk to any foetus caused by exposure to the drug on the other.

7. SSL accepted that Epilim is teratogenic, but denied that the product was defective under the terms of the CPA or at all. SSL relied on the warnings provided to prescribers, from the time of first supply in the UK, regarding the risk of teratogenic effects and the information subsequently provided directly to patients. Such information was regularly reviewed and updated, as approved by the regulatory authorities, to reflect developing scientific and medical knowledge regarding the product. Sanofi also relied on the development risks defence (i.e. that specific risks associated with taking the Epilim were not discoverable at the time the product was put into circulation).

#### Scope of the trial

8. A trial, lasting 18 weeks, was set down for hearing in November 2010. The Court was to consider all issues of liability and causation in relation to 10 Test Cases that were representative of the issues in the litigation (5 cases selected by the Claimants and 5 by SSL). Although the outcome of the Test Cases would not determine the outcome of the remaining claims in the Group Litigation, it would establish findings of law and fact that would narrow the issues to be resolved. If the Claimants succeeded in establishing liability, then their claims for damages would be determined at a later hearing.

#### Conclusion of the litigation

9. Some 2 weeks before the trial was due to start, SSL was notified that the Legal Services Commission’s (LSC) Special Controls Review Panel (SCRIP) had decided to withdraw public funding of the litigation from all of the Claimants. SSL understood that this decision was based on advice that the claims could not succeed. As no alternative funding was forthcoming, the claims were all brought to an end by the middle of 2011.

### **UK SETTLEMENTS**

Sanofi is not aware of any settlements of claims relating to use of its sodium valproate products in pregnancy in the UK.

### **WORLDWIDE LITIGATION AND SETTLEMENTS**

#### Worldwide litigation

Sanofi UK is aware of some claims brought against the company in respect of use in pregnancy of its sodium valproate products. Sanofi UK is unable to comment further as these are the subject of ongoing legal action concerning other jurisdictions in which the medical and legal environments are different.

#### Worldwide settlements

Sanofi is not aware of any settlements of claims relating to use of its sodium valproate products in pregnancy outside of the UK. However, in a number of countries where valproate is used, Sanofi is not responsible for the supply of the relevant products.



## Response to Question 17

**Do you contribute to an administrative (non-litigative) redress scheme anywhere in the world, such as the Nordic pharmaceutical insurance schemes? If so, where, and what are the terms of the contribution? What is your evaluation of the scheme?**

Sanofi is not aware of any such contributions.

### **The French scheme**

The French government, through the 2017 Finance law adopted on 29 December 2016, set up a public fund intended to provide compensation in relation to personal injuries suffered as a result of the prescription of sodium valproate and its derivatives. The compensation scheme was implemented through decrees published on 7 May 2017 and entered into force on 1 June 2017. The arrangements are not legally binding and are made without the need to commence legal proceedings.

The fund was established following a report commissioned by the Ministry of Health into valproate, which raised questions over the actions of the French regulatory authority. Management of the scheme has been assigned to the National Compensation Board for Medical Accidents (ONIAM), a body responsible for the provision of compensation, including to patients suffering from known side effects of medicinal products in cases where no fault could be proven. 10M€ was allocated to the scheme from public funds in 2017 and 70M€ in 2018. The law does not require Sanofi to contribute to the fund and Sanofi has not done so.

The fund is available to provide compensation to persons who have suffered one or more malformations or development disorders as a consequence of the prescription of valproate or one of its derivatives during pregnancy prior to 31 December 2015.

Compensation is assessed through a two-stage procedure involving two committees:

- **The Expert Committee**: determines if the personal injuries claimed resulted from exposure to sodium valproate in utero.
- **The Compensation Committee**: determines the circumstances, causes, nature and extent of the harm suffered and reaches a non-binding conclusion as to which (if any) of the persons considered by the scheme, including healthcare professionals, healthcare establishments, healthcare services or bodies or health product producers, or the State, due to its public health responsibilities, should be asked to make the claimant a compensation offer. In cases where the scheme finds no person liable to pay compensation, ONIAM will make an offer.

## Others

The following manufacturers were invited to respond and declined as they have not marketed valproate containing medicines in the UK.

- Lupin Europe
- Pharsolution (Crescent Pharma)