3rd December 2014

Medicines containing valproate: risk of abnormal pregnancy outcomes (Epilim oral range, Epilim Chrono and Epilim IV range)

Dear Healthcare professional,

This letter is sent in agreement with European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) to inform you of important new information and strengthened warnings related to safety of medicines containing valproate (sodium valproate, valproic acid, valproate semisodium and valpromide), following completion of a Europe-wide review. In agreement with the HPRA, the product information will be updated in due course.

Summary

- **Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases)**
- **Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.**
- **Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.**
- **Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.**
- **You must ensure that all female patients are informed of and understand:**
  - **risks associated with valproate during pregnancy;**
  - **need to use effective contraception;**
  - **need for regular review of treatment;**
  - **the need to rapidly consult if she is planning a pregnancy or becomes pregnant**

Further information on the safety concern and the recommendations

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.

- The risk of congenital malformations is approximately 10 % while 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/or walking, have low intellectual abilities, poor language skills and memory problems[1,2,3,4,5].

- Intelligence quotient (IQ) measured in a study of 6 years old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics[6].
- 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) [7,8,9].

Given these risks, valproate for the treatment of epilepsy or bipolar disorder 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.

Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

If you decide to prescribe valproate to a woman of child-bearing potential, she must use effective contraception during treatment and be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate.

Treatment during pregnancy

If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.

If valproate treatment is continued during the pregnancy:

- the lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment forms;
- Initiate specialised prenatal monitoring in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

The product information will be updated, in due course to reflect our current understanding of the available evidence and to make information as clear as possible and will be available on www.medicines.ie and www.hpra.ie.

It is recommended that pregnancies where the women are taking valproate are enrolled in the Irish Epilepsy & Pregnancy Register, which can be contacted at 1800 320 820 or www.epilepsypregnancyregister.ie.

Educational materials will be made available in due course to healthcare professionals and patients in order to inform about the risks associated with valproate in female children, women of childbearing potential and pregnant women.

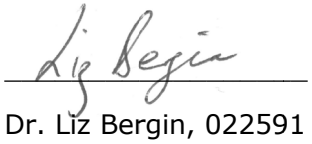
Call for reporting

Please remember that any suspected adverse events should be reported to the Health Products Regulatory Authority (formerly the Irish Medicines Board), via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

This medicinal product is subject to additional monitoring.

Company contact point

Adverse reactions can also be reported directly to Sanofi: email IEPharmacovigilance@sanofi.com or at telephone number (01) 4035600. Our medical information department can be contacted for further information at IEMedinfo@sanofi.com or at telephone number (01) 4035600.



Dr. Liz Bergin, 022591

Medical Director, Sanofi Ireland

Annexes

Annex 1: Concerned Products:

Epilim Crushable Tablets 540/150/1, Epilim Enteric Gastro-resistant Coated Tablets 540/150/2 & 540/150/3, Epilim Chronosphere Prolonged Release Granules 540/150/5, 540/150/6, 540/150/7, 540/150/8, 540/150/9, Epilim Chrono Prolonged Release Tablets 540/150/10, 540/150/11, 540/150/12, Epilim Intravenous Powder and Solvent for solution for injection or infusion 540/150/13, Epilim Liquid Oral Solution 540/150/14, Epilim Syrup Oral Solution 540/150/15, Depakote Tablets 04425/0199.

Annex 2: Updated Product Information:

For the products listed in Annex 1, the following sections of the SmPC will be updated: Top of SmPC (▼ Black Triangle added to indicate the medicinal product is subject to additional monitoring), Section 4.2, 4.4, 4.4, 4.6 & 4.8. The Patient leaflet will also be updated. Please see the enclosure for details.

Further information can be found on the EMA website (www.ema.europa.eu) including the assessment report from the PRAC.

References

[1] Meador K, Reynolds MW, Crean S et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81(1):1-13.

[2] Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, Liporace JD, Sam M, Kalayjian LA, Thurman DJ, Moore E, Loring DW; NEAD Study Group. Antiepileptic drug use in women of childbearing age. Epilepsy Behav. 2009;15(3):339-43.

[3] Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology. 2008;71(23):1923-4.

[4] Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. Epilepsia. 2007 Dec;48(12):2234-40.

[5] Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011 July;96(7):643-7.

[6] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244-52.

[7] Christensen J, Grønborg TK, Sørensen MJ et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013; 309(16):1696-703.

[8] Cohen MJ, Meador KJ, Browning N, May R, Baker GA, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD study group. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. Epilepsy Behav. 2013;29(2):308-15.

[9] Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240-246

Annex II

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:
These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Concerned Products:

Epilim Crushable Tablets 540/150/1,
Epilim Enteric Gastro-resistant Coated Tablets 540/150/2 & 540/150/3,
Epilim Chronosphere Prolonged Release Granules 540/150/5, 540/150/6, 540/150/7, 540/150/8, 540/150/9,
Epilim Chrono Prolonged Release Tablets 540/150/10, 540/150/11, 540/150/12,
Epilim Intravenous Powder and Solvent for solution for injection or infusion 540/150/13,
Epilim Liquid Oral Solution 540/150/14,
Epilim Syrup Oral Solution 540/150/15,
Depakote Tablets 04425/0199.

SUMMARY OF PRODUCT CHARACTERISTICS

[This statement below should be inserted at the top of the SmPC for all products referred to on PageI]

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

[…]

[For all products in referenced on Page 1, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]

[…]

Section 4.2 Posology and method of administration

[…]

Female children, female adolescents, women of childbearing potential and pregnant women

<Invented name> should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably <Invented name> 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 Special warnings and precautions for use

[…] [This section should be amended to include the following box]

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

<Invented name> 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 <Invented name> 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 <Invented name> 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 or bipolar disorder.

[…]

Section 4.6 Fertility, pregnancy and lactation

[…] [This section should be amended to include the following wording]

<Invented name> 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 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 epilepsy or bipolar disorder. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

[For all products referred to in Page I]

<u>Risk in the neonate</u>

- 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.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding

Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from <Invented name> therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.
[…]

Section 4.8 Undesirable effects
[…]

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).
[…]

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

PACKAGE LEAFLET

[This statement below should be inserted at the top of the package leaflet for all products referred to in Page 1]

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.
[…]

WARNING

Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.

Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms seem the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

[…]

2. What you need to know before you take <Invented name>

[…]

Pregnancy, breast feeding and fertility
[This section should be amended to include the below wording]
[…]

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in ever 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.

- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

FIRST PRESCRIPTION
If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.

- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY
If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception

- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY
If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/bipolar disorder is controlled and the risks to your baby are reduced.

- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

[This sentence below should be adapted to National requirements]

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.
[…]

3. How to take <Invented name>
[…]

<Invented name> treatment must be started and supervised by a doctor specialised in the treatment of epilepsy or bipolar disorder.
[…]

4. Possible side effects

[This section should be amended to include the below wording in all indications]
[…]

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.