Ref: 04/2018/MZ
13.07.2018

Direct Healthcare Professional Communication

Valproate: new restrictions on use; pregnancy prevention programme to be put in place

Dear Healthcare professional,

The Central Procurement & Supplies Unit (CPSU), Sanofi Malta Limited and Wockhardt UK Limited in agreement with the European Medicines Agency and the Malta Medicines Authority would like to inform you of the following:

Summary

Teratogenicity

- Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated
- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and of congenital malformations (in approximately 10% of cases)
- In pregnancy and in women of childbearing potential new contraindications apply:
    - In epilepsy
        - valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
        - valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are met
- For women of childbearing potential currently using valproate the treatment may need to be re-evaluated to decide if the conditions of the pregnancy prevention programme (described below) are fulfilled

Key elements of the Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks
- The potential for pregnancy is assessed for all female patients
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to valproate in utero
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception, without interruption during the entire duration of treatment with valproate
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy

- The patient understands the need to consult her physician as soon as she is planning a pregnancy to ensure timely discussion and switching to alternative treatment prior to conception, and before contraception is discontinued
- The patient understands the need to urgently consult her physician in case of pregnancy
- The patient has received the patient guide
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form)

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

More detailed instructions related to the following topics are provided in the annex of this letter:

- The use of valproate in female children
- The need to rule out pregnancy before valproate initiation
- The use of effective contraception
- The annual treatment review by a specialist
- The use of the annual risk acknowledgement form (at treatment initiation and during treatment review, at least annually)
- What to do with valproate treatment at the time of pregnancy planning and during pregnancy
- Specific actions to be taken by the pharmacist such as provision of the patient card

The product information of all valproate-containing products will be updated accordingly.

It is recommended that pregnant women taking valproate are enrolled in registries of antiepileptic drugs and pregnancy or such data collection at a national level.

Educational materials

To assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, a Patient Card (on the outer package), a Patient Guide, an annual risk acknowledgment form, and a Guide for prescribers, pharmacists and other healthcare providers involved in the care of women of childbearing potential using valproate will be available to inform healthcare professionals and patients/caregivers on the risks of valproate and the conditions for use.

A patient guide and patient card should be provided to all women of childbearing potential using valproate. An annual risk acknowledgement form needs to be used by the specialists at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Patient card, patient guide, annual risk acknowledgment form, and guide for healthcare professionals are available from the Malta Medicines Authority website.

Background information

In 2014 the warnings and restrictions on the use of valproate medicines in women and girls were strengthened, to minimise the risk of malformations and developmental problems in babies exposed to valproate in the womb. EMA's safety experts, the Pharmacovigilance Risk Assessment Committee (PRAC) has now reviewed the impact of these measures following concerns that the measures were not sufficiently effective in increasing awareness and reducing valproate use appropriately during pregnancy. The PRAC found these concerns to be well founded and has therefore introduced new measures.

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 in up to 40%, early development such as talking, and walking is delayed and they have low intellectual abilities, poor language skills and memory problems[1],[2,3,4,5]
- Intelligence quotient (IQ) measured in a study of 6-year-old children with a history of valproate exposure in utero was on average 7-10 points lower than 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[7]
- Limited data suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[8]

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with valproate medicines in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

▼ Valproate is subject to additional monitoring. This will allow quick identification of new safety information.

References

[1] Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.

[2] Bromley RL, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October; 51(10):2058–65.

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[4] Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009;360(16):1597–1605.

[5] Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008 (13):229–236.

[6] Meador KJ, et al. 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 et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696–1703.

[8] Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive and emotional/behavioural functioning at age 3 years. *Epilepsy Behav*. 2011; 22(2):240–246.

Company contact points

Company	Product name	Email	Phone
CPSU	Epilim 100mg Crushable Tablets	richard.despott@gov.mt	+356 23439150
Sanofi Malta Limited	Epilim 200 Gastro-resistant Tablets Epilim 500 Gastro-resistant Tablets Epilim Intravenous Epilim Liquid, 200mg/5ml, liquid Epilim Chrono 200 Controlled Release Epilim Chrono 500 Controlled Release Epilim Chrono 300 Controlled Release	Graziella.gravino@sanofi.com	+356 21493022
Wockhardt UK Limited	Sodium Valproate (400mg/4ml) Solution for Inj/Inf 100mg/ml Sodium Valproate (1000mg/10ml) Solution for Inj/Inf 100mg/ml	Drug.Safety@wockhardt.co.uk	+44 1978 661 261

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Central Procurement & Supplies Unit (CPSU), Sanofi Malta Limited and Wockhardt UK Limited

Annex – Conditions of the Pregnancy Prevention Programme (PPP)

The following information should be read in conjunction with the conditions of the pregnancy prevention programme which are described in the letter above.

Female children

- Valproate should not be prescribed to female children or women of child bearing potential, unless there is no suitable alternative treatment
- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Efforts should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

For the indication epilepsy, 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. If switching is not possible, the woman should receive further counselling regarding the valproate risks for unborn child to support her informed decision making regarding family planning.

In case of pregnancy

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment.

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. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of 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.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy. Specialized 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.

Pharmacists must ensure that

- The patient card is provided with every valproate dispensing and that the patients understand its content.
- Reinforce the safety messages including the need for effective contraception.
- The patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.
- Dispense valproate in the original package with an outer warning. In some countries where valproate might be unpacked in pharmacies, unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.