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HPRA DRUG SAFETY
NEWSLETTER

87TH EDITION

Valproate (Epilim): New contraindication, strengthened warnings and measures to prevent exposure during pregnancy

Valproate-containing medicines (licensed in Ireland as Epilim) are now contraindicated in women of childbearing potential unless the terms of a special pregnancy prevention programme are followed. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate has high teratogenic potential and children born to mothers who take valproate during pregnancy have a 30-40% risk of developmental disability and a 10% risk of birth defects.

In 2014 the warnings and restrictions regarding the use of valproate in women and girls were strengthened to minimise these risks. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has now reviewed the impact of these measures following concerns that they were not sufficiently effective in increasing awareness and reducing exposure to valproate use during pregnancy. The PRAC considered these concerns were well founded and has recommended important new contraindications, strengthened warnings and measures to further prevent valproate exposure during pregnancy.

Following input from patients during the PRAC review and nationally, it was highlighted on several occasions that in many cases patients are not aware that Epilim contains the active ingredient sodium valproate. HCPs should therefore ensure that patients are made aware that the brand name in Ireland is 'Epilim'.

Advice to Healthcare Professionals

- Children exposed to valproate in utero are at high risk of serious developmental disorders (in up to 30-40% of cases) and of congenital malformations (in approximately 10% of cases).
- Valproate should only be used in female children, girls and women of childbearing potential if other treatments are ineffective or not tolerated.
- 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 all the conditions of the pregnancy prevention programme (described below) are met.

  - In bipolar disorder
    - valproate is contraindicated in pregnancy.
    - valproate is contraindicated in women of childbearing potential, unless all the conditions of the pregnancy prevention programme (described below) are met.
- In female children and women of childbearing potential valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
- Healthcare professionals should prescribe and dispense valproate according to the Valproate pregnancy prevention programme (described below).
- For women of child bearing potential who are currently using valproate, prescribers should re-evaluate treatment to ensure that the conditions of the pregnancy prevention programme are met and that valproate remains the most appropriate therapeutic option for them.
- Prescribers should discuss the risk with their patients and ensure that relevant patients receive and understand the patient guide.
- Pharmacists should ensure that relevant patients are aware of and understand the risk and provide them with the package leaflet and patient card when dispensing valproate.

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Key elements of the new Valproate Pregnancy Prevention Programme

The prescriber should ensure that:

- The potential for pregnancy is assessed for all female patients.
- For each patient, individual circumstances should be evaluated and the patient should be involved in the discussion to guarantee her engagement, discuss her therapeutic options and to ensure she understands the risks and the measures needed to minimise the risks.
- The patient understands the need to undergo pregnancy testing before commencing treatment and during treatment, as needed.
- The patient has fully understood and acknowledged the risks of congenital malformations and neurodevelopment disorders associated with the use of valproate, including the magnitude of these risks for children exposed to valproate in utero.
- The patient is counselled and understands the need for effective contraception throughout treatment and is capable of complying with this need, without interruption during the entire duration of treatment.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of her condition.
- 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 and understood the patient guide and other materials designed to provide her with information on the risks and necessary precautions associated with valproate use (see below).
- The patient has acknowledged that she has understood the risks and necessary precautions associated with valproate use by signing the Annual Risk Acknowledgement Form (see below).

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

Annual treatment reviews

The prescribing specialist should review the patient at least annually and decide whether valproate remains 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 test

Pregnancy must be excluded before treatment with valproate commences. A negative pregnancy test result in women of child-bearing potential, confirmed by a healthcare provider, is required to rule out unintended use in pregnancy.

Contraception

Women taking valproate who are of child bearing potential must use effective contraception without interruption for the entire duration of treatment with valproate. At least one effective method of contraception (e.g. 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 and the patient should be fully involved in the discussion regarding the method of contraception chosen, to guarantee her engagement and compliance with the chosen measures. The patient should be referred for contraceptive advice if not using effective contraception currently.

Pregnancy planning

If a woman being treated with valproate for epilepsy is planning a pregnancy, then a specialist must reassess the need for valproate and consider alternative therapies. Every effort should be made to switch the patient to another treatment prior to conception and before contraception is discontinued.

If a women is being treated with valproate for bipolar disorder the specialist should be consulted prior to conception so that treatment with valproate can be discontinued and an alternative treatment commenced, if necessary, before contraception is discontinued.

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In case of pregnancy

If a woman using valproate becomes pregnant, she must immediately be seen by a specialist to review and re-evaluate her treatment, to consider alternative treatment options and switching. In epilepsy, maternal tonic-clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and baby.

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 does into at least two single doses. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

Patients (and their partners) with a valproate exposed pregnancy should be referred to an appropriate specialist for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects and other physical malformations.

Although folate supplementation before the pregnancy may reduce the risk of neural tube defects which may occur in all pregnancies, available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Female children:

- Valproate should not be prescribed to girls unless there is no suitable alternative.
- The prescribing specialist must ensure that parents/caregivers of girls being prescribed valproate understand the need to contact the specialist once the child begins menstruation.
- The prescribing specialist must ensure that patients/caregivers of girls who have commenced menstruation 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.
- The prescribing specialist must reassess the need for valproate therapy annually in girls who have commenced menstruation and consider alternative treatment options. Patients should be switched to alternative treatment before they reach adulthood. If valproate is the only suitable treatment, the need for effective contraception and all conditions of the pregnancy prevention programme should be discussed.

Pharmacists should ensure that:

- The package leaflet is provided to the patient every time valproate (Epilim) is dispensed.
- The patient card is provided to the patient every time valproate is dispensed and the patient understands its content.
- Valproate is dispensed in the original package with the outer warning. In situations where the original package cannot be provided, always provide a copy of the package leaflet and the patient card.
- The patient is advised that they should not stop valproate but to immediately contact their doctor to arrange urgent review with their specialist in case of a planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients to mitigate the risk of exposure to valproate during pregnancy, revised educational materials are being developed and will be circulated by the marketing authorisation holder (MAH i.e. license holder) for Epilim following approval by the HPRA. The revised educational materials will include:

- A guide for prescribers, pharmacists and other healthcare professionals potentially involved in the care of girls and women of childbearing potential treated with valproate.
- A guide for patients which the prescriber should provide to all girls and women of child-bearing potential who start treatment with valproate or who are already on treatment
- A patient reminder card attached to the outer packaging of valproate to facilitate discussions between the pharmacist and the patient each time the medicine is dispensed.
- These materials will shortly be approved by the HPRA and available on the HPRA website (www.hpra.ie) and from the Marketing Authorisation Holder (MAH) for Epilim. In addition, the outer packaging of all valproate containing medicines will be updated to include a visual warning about the risks of pregnancy. The warning will include boxed text and a symbol/pictogram.

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Additional Background Information

In 2014, the HPRA advised against prescribing valproate-containing medicines in girls and women of childbearing potential unless other treatments are ineffective or not tolerated. The outcome of the 2014 review was communicated to healthcare professionals in December 2014 via the HPRA Drug Safety Newsletter Edition 65 and a Direct Healthcare Professional Communication (DHPC) circulated by the Marketing Authorisation Holder (MAH) following approval by the HPRA.

In August 2016, the HPRA issued further communication materials and resources to support discussion of these risks with women and girls of childbearing potential who take valproate. Educational materials developed by the Marketing Authorisation Holder (MAH), following approval by the HPRA to inform healthcare professionals and patients about these risks are also available from the HPRA website and the MAH. The availability and a description of these educational materials were communicated in August 2016 via the HPRA Drug Safety Newsletter Edition 76.

In March 2017, the EMA's PRAC initiated a new review specifically to examine the impact of the risk minimisation measures recommended in the 2014 review. Concerns had been raised in some member states about how effective these measures have been in practice at increasing awareness of the risk of malformations and developmental problems in babies who are exposed to valproate in utero. The PRAC review has now concluded and the main measures recommended are described above. The HPRA is currently liaising with relevant national stakeholders (Department of Health (DoH), Health Services Executive (HSE), specialists in neurology, psychiatry and primary care, the Pharmaceutical Society of Ireland (PSI), Epilepsy Ireland and Organisation for Anti-Convulsant Syndrome (OACs) to ensure timely implementation of all of these recommendations nationally.

At EU level, the scientific (PRAC) and regulatory (Co-ordination Group for Mutual Recognition and Decentralised Procedures for human medicines (CMDh)) committees reviews have concluded. The recommendations from the review will now be sent to the European Commission for a legally binding decision to complete the regulatory process.

A Direct Healthcare Professional Communication (DHPC) has been sent by the MAH following HPRA approval and is accessible from the HPRA website.

Key Message

Children exposed to valproate in utero are at a high risk of serious developmental disorders (up to 30-40%) and of congenital malformations (in approximately 10% of cases).

A valproate pregnancy prevention programme is being implemented nationally and across the EU.

In pregnancy and in women of childbearing potential, new contraindications apply:

- Valproate is contraindicated in women of childbearing potential, unless all conditions of the pregnancy prevention programme are met.
- In epilepsy, valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.
- In bipolar disorder, valproate is contraindicated in pregnancy.

For women of childbearing potential currently using valproate, treatment may need to be re-evaluated to ensure that the conditions of the pregnancy prevention programme are met.

A Direct Healthcare Professional Communication (DHPC) has been circulated by the MAH, following approval by the HPRA, to relevant healthcare professionals.

Over the coming weeks, the educational materials will be updated with the new recommendations and will be available from the HPRA website (www.hpra.ie).

All suspected adverse reactions associated with valproate-containing medicines should be reported to the HPRA via the usual methods (www.hpra.ie).

Valproate-containing medicines are approved nationally in Ireland in various presentations, under the brand name Epilim, to treat epilepsy and bipolar disorder. Further information on valproate-containing medicines is available from www.hpra.ie.

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Xofigo (radium-223-dichloride)	Contraindication in combination with abiraterone acetate and prednisolone/prednisone

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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