NEW INFORMATION – FEBRUARY 2022

GUIDE FOR HEALTHCARE PROFESSIONALS

Information on the risks of Valproate▼ (Epilim) use in girls (of any age), women of childbearing potential and pregnant women.

prevent
valproate pregnancy
prevention programme

Read this booklet carefully before prescribing valproate to girls (of any age) and women of childbearing potential.

This Guide is a risk minimisation measure part of **prevent** – the valproate pregnancy prevention programme, aimed at minimising pregnancy exposure during treatment with valproate.

The information in this Guide has been approved by the Medicines Authority on 26 Oct 2022

PURPOSE OF THIS GUIDE

This Guide for healthcare professionals (HCPs) is an educational material, part of **prevent** – the **valproate pregnancy prevention programme**, which is directed at both healthcare professionals and patients.

Its objective is to provide information about the teratogenic risks associated with the use of valproate during pregnancy, the actions necessary to minimise the risks to your patients, and to ensure your patient has an adequate level of understanding of the risk.

It provides up-to-date information about the risks of **congenital malformations** and **neuro-developmental disorders** in children exposed to valproate during pregnancy.

The nature of the risks for children exposed to valproate during pregnancy are the same irrespective of the indication for which valproate has been prescribed. Therefore, the risk minimisation measures described in this Guide apply to the use of valproate regardless of the indication.

HCPs targeted by this Guide include, but are not limited to: specialists involved in the treatment of epilepsy or bipolar disorder, general practitioners and pharmacists.

The valproate educational materials developed specifically for girls (of any age) and women of childbearing potential treated with valproate comprise:

- The Patient Guide
- The Annual Risk Acknowledgment Form, and
- The Patient Card.

Use this Guide together with the Patient Guide.

CONTENTS

1. Conditions of valproate prescription: prevent – the pregnancy prevention programme

Valproate is an effective treatment for epilepsy and bipolar disorder.

In girls and women of childbearing potential* valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.

Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate may be initiated in **girls and women of childbearing potential** only if the conditions of **prevent** – the valproate pregnancy prevention programme (outlined below) are fulfilled.

How do I implement the prevent programme?

Specialists

- Discuss the risks with the patient (or parent/caregiver/responsible person)
- Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued
- Arrange for highly effective** contraception for women of childbearing potential before the first prescription is issued
- Complete the Annual Risk Acknowledgment Form with patient (or parent/caregiver/responsible person); give them a copy and send a copy to the GP
- See the patient urgently if referred back in case of unplanned pregnancy or if she wants to plan a pregnancy
- Provide a copy of the Patient Guide to the patient (or parent/caregiver/responsible person)

General practitioners

- Ensure continuous use of highly effective contraception in all women of childbearing potential (consider the need for pregnancy testing if not a highly effective method)
- Check that all patients have an up to date, signed, Annual Risk Acknowledgement Form each time a repeat prescription is issued
- Ensure the patient is referred back to the specialist for review, annually
- Refer back to the specialist urgently in case of unplanned pregnancy or where a patient wants to plan a pregnancy.

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.

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.

Highly effective contraception is considered for regulatory purposes to be those user independent methods such as the long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogen-only implant (IMP) and female sterilisation, all of which have a failure rate of less than 1% with typical use. The progesterone-only injectable is reported to have a typical use failure rate of 6 pregnancies per 100 women per year of typical use compared to 0.2 pregnancies with perfect use (thought to be due to the 3 monthly requirement for re-injection and lack of compliance with this).

User dependent methods such as the condom, cap, diaphragm, combined oral contraceptive pill (COC) or progestogen-only contraceptive pill (POP) and fertility awareness based methods are not considered highly effective since the typical use incorporates user failure risks.

For children or for patients without the capacity to make an informed decision, provide the information and advice on highly effective methods of contraception and on the use of valproate during pregnancy to their parents / legal guardian / caregiver and make sure they clearly understand the content.

Please read the most up-to-date version of the Summary of Product Characteristics before prescribing valproate.

* A woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant.
** At least one highly effective method of contraception (preferably a user independent form such as an intrauterine 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 highly effective contraception.

2. Treatment of girls (of any age) and women of childbearing potential with valproate – actions for healthcare professionals

Actions for general practitioners

Valproate is contraindicated in women of childbearing potential unless the conditions of **prevent** – the valproate pregnancy prevention programme are fulfilled.

1. Existing female patients

- Identify all women of childbearing potential on valproate
- Recall any women who may be of childbearing potential and arrange for contraception if not already using contraception
- Inform her of the known risks and ensure that she understands she must not get pregnant whilst taking valproate
- Tell her to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant
- Refer to her specialist† (unless she has seen one recently and is on **prevent**)
- Arrange to see each woman of childbearing potential after specialist review and ensure she is on **prevent**, i.e. ensure that:
  - she has the Patient Guide and has a copy of the Annual Risk Acknowledgment Form signed by the specialist
  - you file a copy of the signed Annual Risk Acknowledgment Form in her medical records
  - she is using contraception and understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception
- Remind her that she will need to see her specialist at least every year while taking valproate medicines and arrange for referral as necessary.

† Specialist prescriber is defined as a consultant psychiatrist or a consultant neurologist who regularly manages bipolar disorder or complex epilepsy.

2. **New female patient – women of childbearing potential**
   - Refer her to the relevant specialist† for diagnosis and to initiate treatment if appropriate
   - Arrange to see each woman of childbearing potential after specialist review and ensure she is on **prevent**, i.e. ensure that:
     - she has the Patient Guide and has a copy of the Annual Risk Acknowledgment Form signed by the specialist
     - you file a copy of the signed Annual Risk Acknowledgment Form in her medical records
     - she is using contraception and understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception
   - Remind her that she will need to see her specialist at least every year while taking valproate medicines and arrange for referral as necessary
   - Tell her to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant.
3. **Women of childbearing potential who are planning to become pregnant**
   - Inform her not to stop contraception or valproate until told to by her specialist
   - Refer to the specialist who is managing her condition.
4. **Patient with unplanned pregnancy**
   - Inform her not to stop valproate
   - Refer her to a specialist and ask for her to be seen urgently (within days)
   - It is recommended that pregnant women taking valproate are enrolled in the Irish Epilepsy and Pregnancy Register (www.epilepsypregnancyregister.ie).

Actions for specialist prescribers

Valproate is contraindicated in women of childbearing potential unless the conditions of **prevent** – the valproate pregnancy prevention programme are fulfilled.

1. **Existing female patients**
   - Review women who may be of childbearing potential
   - Continue treatment with valproate only if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test.

† Specialist prescriber is defined as a consultant psychiatrist or a consultant neurologist who regularly manages bipolar disorder or complex epilepsy.

   - Discuss the need for her to be on the **prevent** programme if she is to continue taking valproate:
     - Ensure she understands the risks to the unborn child of using valproate during pregnancy and provide the Patient Guide
     - Ensure she understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception
     - Complete and sign the Annual Risk Acknowledgment Form (at every annual visit); give a copy to her and send one to her GP
     - Refer for contraception services as needed
     - Ensure that you invite all women on **prevent** for an annual review.
2. **New female patient – women of childbearing potential**
   - Start treatment with valproate only if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test
   - Assess potential for pregnancy and if necessary discuss the need for her to be on the **prevent** programme if she is to take valproate:
     - Ensure she understands the risks to the unborn child of using valproate during pregnancy and provide the Patient Guide
     - Ensure she understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception
     - Complete and sign the Annual Risk Acknowledgment Form (at every annual visit); give a copy to her and send one to her GP
     - Refer for contraception services as needed.
     - Ensure that you invite all women on **prevent** for an annual review
3. **Women of childbearing potential planning to become pregnant**
   - Ensure she understands the risks of valproate in pregnancy
   - Switch valproate to another therapeutic option
   - Tell her not to stop contraception until the switch is achieved and she is no longer taking valproate
   - If switching is not possible refer for counselling about the risks.

4. Patients with an unplanned pregnancy

- Women presenting with an unplanned pregnancy should have their treatment switched
- Women with epilepsy who have to continue treatment in pregnancy (i.e. if switching to an alternative treatment is not possible) should be referred to an obstetrician
- It is recommended that pregnant women taking valproate are enrolled in the Irish Epilepsy and Pregnancy Register (www.epilepsypregnancyregister.ie).

Actions for pharmacists

- 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 with an outer warning. Dispensing outside of original packaging should be avoided. In situations where this cannot be avoided, always provide a copy of the package leaflet and add a sticker with the warning to the outer packaging
- If a woman of childbearing potential reports that she is not taking highly effective contraception, refer them to their GP (including by contacting the GP if necessary).

3. Switching or discontinuing valproate

Patients with bipolar disorder

Valproate is contraindicated in pregnancy.

Valproate is contraindicated in women of childbearing potential unless the conditions of **prevent** – the valproate pregnancy prevention programme are fulfilled (see section 1 in this Guide).

If a woman is planning to become pregnant, the prescriber must switch the patient to another treatment. Switching should be achieved prior to conception and before contraception is discontinued.

If a woman becomes pregnant, treatment with valproate must be switched and discontinued to another treatment.

Patients with 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 **prevent** – the valproate pregnancy prevention programme are fulfilled (see section 1 in this Guide).

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 a woman becomes pregnant on valproate, she must be immediately referred to a specialist to consider alternative treatment options.

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 prenatal medicine
- Enrol pregnant women taking valproate in the Irish Epilepsy and Pregnancy Register (www.epilepsypregnancyregister.ie).

4. Information on congenital malformations and on neurodevelopmental disorders

Valproate contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations.

1. Congenital malformations

A meta-analysis (including registries and cohort studies) showed that about 11%[1] of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2-3%). The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate. This risk is dose-dependent in valproate monotherapy, and available data suggest it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.

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.

In utero exposure to valproate may also result in:

- unilateral or bilateral hearing impairment or deafness, that may not be reversible[2],
- eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

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.

2. Neurodevelopmental 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 of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from the general population or born to untreated epileptic mothers.

The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, studies[3-6] in preschool children show that up to 30–40% of children with a history of valproate exposure *in utero* 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 years old) with a history of valproate exposure *in utero* was on average 7–10 points lower than children exposed to other antiepileptic drugs[7]. Although the role of confounding factors cannot be ruled out, 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 from a population-based study show that children with a history of valproate exposure *in utero* are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study[8].

Available data from another population-based study show that children with a history of valproate exposure *in utero* are at increased risk of developing attention deficit hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study[9].

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. Foch C, Araujo M, Weckel A, Damase-Michel C, Montastruc JL, Benevent J, et al. In utero drug exposure and hearing impairment in 2-year-old children A case-control study using the EFEMERIS database. *Int J Pediatr Otorhinolaryngol*. 2018 Oct;113: 192–197.
3. Bromley RL, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October;51(10):2058–2065.
4. Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;96:643–647.
5. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009;360(16):1597–1605.
6. Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008 (13):229–236.
7. 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):244–252.
8. Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696–1703.
9. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. *JAMA New Open*. 2019;2(1): e186606.

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