GUIDE FOR HEALTHCARE PROFESSIONALS

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

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

This Guide is a risk minimisation measure aimed at minimising pregnancy exposure during treatment with valproate.

This guide also contains information on switching pregnant women from valproate.

PURPOSE OF THIS GUIDE

This Guide for healthcare professionals (HCPs) is an educational materia 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, gynaecologists/obstetricians, midwives, nurses, pharmacists and emergency physicians.

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

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.

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 (outlined below) are fulfilled.

How to implement?

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 (within days) 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 Acknowledgment of Risk 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 (within days) in case of unplanned pregnancy or where a patient wants to plan a pregnancy.

* a woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant.

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/caregiver/responsible person 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.

** 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 (outlined below) 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
   - Arrange to see each woman of childbearing potential after specialist review and 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 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, if on valproate, ensure:
        - she has the Patient Guide and has a copy of the Annual Risk Acknowledgment Form signed by the specialist, and file a copy of the form in her medical records
        - 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).

Actions for specialist prescribers

Valproate is contraindicated in women of childbearing potential unless the conditions (outlined below) 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
    - Discuss with her 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 initiation and 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 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 with her 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 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 for appropriate monitoring.

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

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. 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 them to their GP (including by contacting the GP if necessary).

Actions for gynaecologists/obstetricians, midwives and nurses

- Provide counselling on contraception methods and pregnancy planning
- Provide information about the risks of using valproate during pregnancy
- When a patient consults for pregnancy refer her and her partner to her prescriber and to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Actions for emergency physicians

- Ensure that any woman of childbearing potential using valproate is referred to her specialist for assessment
- If she is pregnant, ensure that she is referred for urgent review (within days).

3. Switching or discontinuing valproate

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 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.

General considerations for patients with epilepsy:

Issued by Task Force of Commission of European Affairs of International League Against Epilepsy (CEA-ILAE) and European Academy of Neurology (EAN):

- "Drug withdrawal is usually undertaken gradually over weeks to months, which allows an opportunity to identify the likely minimum required dose should a seizure occur during drug withdrawal."
- "The switch of valproate to an alternative treatment will commonly occur over at least 2–3 months. The new medication is usually first gradually introduced as add on to valproate. This can take up to 6 weeks to reach a potentially effective dose of the new treatment; thereafter an attempt can be made to gradually withdraw valproate."

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:

- There is no dose threshold considered to be without any risk. However, the risk of birth defects and developmental disorders is higher at greater doses
- 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.

4. Information on congenital malformations and on developmental disorders

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

1. Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) have shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% confidence interval: 8.16–13.29%). This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2–3%[3]. Available data show that the risk is dose-dependent. The risk is greatest at higher doses (above 1g daily). A threshold dose below which no risk exists cannot be established based on available data.

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.

Folic acid supplementation may decrease the general risk of neural tube defects but there is some evidence that it does not reduce the risk of birth defects associated with in utero valproate exposure

2. Developmental disorders

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 regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies[4-7] in preschool children show that 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[8]. 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 show that children with a history of valproate exposure *in utero* are at increased risk of autistic spectrum disorder (an approximately three-fold increased risk) and childhood autism (an approximately five-fold increased risk) compared with the general study population[9].

Limited data suggest that children with a history of valproate exposure *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).[10]

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Information about valproate use can also be found online at www.medicinesauthority.gov.mt/rmm

Adverse event reporting

▼ This medicinal product is subject to additional monitoring. Adverse events should be reported. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, Sir Temi Zammit Buildings,Malta Life Sciences Park, San Gwann S.N 3000 Malta or sent by email to postlicensing.medicinesauthority@gov.mt