NEW INFORMATION – NOVEMBER 2019

GUIDE FOR HEALTHCARE PROFESSIONALS

Information on the risks of valproate ▼ (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell, Valpal & Belvo) use in girls (of any age) and women of childbearing potential.

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.

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

It is recommended that pregnant women taking antiepileptic drugs in general, and valproate in particular, are enrolled in the UK Epilepsy and Pregnancy Register (http://www.epilepsyandpregnancy.co.uk). This should be done as early as possible in the pregnancy, before the outcome is known.

Medicines & Healthcare products Regulatory Agency

The information in this Guide has been approved by the MHRA.

PURPOSE OF THIS GUIDE

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

It provides up-to-date information about the risks of serious **congenital malformations** and **neuro-developmental disorders** in children of mothers exposed to valproate during pregnancy. It also describes the actions necessary to minimise the risks to your patients, and to ensure your patient has an adequate understanding of the risk.

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 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 HCP Guide together with the Patient Guide.

What's New in this Guide?

The main changes made from the previous version (dated May 2018) are as follows:

- New section: Definition of Specialist Prescribers (page 6)
- New section "Contraception" (page 7)
- New section "Does **prevent** apply to my patient?" (page 8)
- Clarification that the provisions of **prevent** apply when a patient is being switched from valproate to another treatment (page 12)

The changes made are to clarify the existing Regulatory situation and not due to new advice.

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.

A woman of childbearing potential (WOCBP) is a pre-menopausal female (from menarche to menopause) who is capable of becoming pregnant.

Valproate may be initiated only if the conditions of **prevent** – the valproate pregnancy prevention programme (outlined below) are fulfilled.

The conditions of **prevent** need to be maintained throughout the period of use of valproate. This includes patients who are switching to a therapy other than valproate – the conditions of **prevent** should be continued until valproate is discontinued.

How to implement **prevent**

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 annual review.
- Refer to the specialist urgently (within days) in case of unplanned pregnancy or where a patient wants to plan a pregnancy.

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 the 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).

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.

Definition of Specialist prescribers:

A specialist prescriber, who initiates treatment, is a consultant neurologist, psychiatrist or paediatrician who regularly manages complex epilepsy or bipolar disorder.

Activities to implement **prevent** may be carried out by other healthcare professionals as part of a consultant led team. For example, specialist nurses who manage these conditions are integral to the process and should be considered as specialists for this situation. There may be different levels of responsibility depending on whether the nurse holds an independent prescribing qualification or not.

Joint clinical guidance has been issued (29 March 2019) on behalf of the Royal College of GPs, Association of British Neurologists and the Royal College of Physicians, providing information in this area and indicates who should be responsible, but that prescribing decisions and switching medicines should be under the guidance and care of a consultant.

Contraception:

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.

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%[1] with typical use.

Progestogen-only injections have a typical-use failure rate of 6%[1], but this may be due to repeat injections being administered late. Progestogen-only injections may be considered as highly effective if repeat injections are documented as having been administered on schedule by a healthcare professional.

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 of failure. COC or POP methods have a typical failure rate of around 9%[1] – they must be used together with a barrier method of contraception and frequent pregnancy testing should be carried out.

Pregnancy tests may not detect an early pregnancy that has occurred after unprotected sex in the preceding 3 weeks. Therefore, women should have a repeat pregnancy test 3 weeks after starting a new contraceptive method if there was any risk of pregnancy at the start of the contraceptive method, even if the first test was negative.

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.

Does **prevent** apply to my patient?

Women of childbearing potential (from menarche to menopause) who are taking any medicine containing valproate, regardless of the indication, should fulfil all the requirements of **prevent**. The only exception is when the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy:

- The absence of risk of pregnancy may be permanent (e.g., post-menopausal patients or those after hysterectomy).
- The absence of risk may change (e.g., the patient is pre-menarchal).

The reasons why the patient does not need to be enrolled on **prevent** should be documented on the Annual Risk Acknowledgment Form. The patient or responsible person should countersign the Annual Risk Acknowledgment Form to confirm the exception is in place and that risks have been discussed.

If the absence of risk may change, the date for the next annual review must be documented and the patient or the patient's family/carers asked to contact the specialist rapidly if the situation changes before that date.

Girls who have not yet reached menarche DO NOT need to be on '**prevent**', but they and their parent/ carer / responsible person need to be aware of the risks for the future.

A copy of the Patient Guide should be provided and the responsible person reminded to contact the specialist or GP to arrange for review of treatment as soon as menarche occurs.

WARNING:

- Prescribing valproate to a woman of childbearing potential without fulfilling the conditions of the pregnancy prevention programme is contraindicated and represents an unlicensed use of the drug.
- Use of valproate during pregnancy for epilepsy (unless there is no suitable alternative treatment), and for bipolar disorder are both contraindicated. This is the case even when treatment is based on an informed choice made by the patient.
- Prescribers are expected to follow the General Medical Council's guidance in "Good practice in prescribing and managing medicines and devices". You must document in the patient's clinical record your reason for any unlicensed use and that you have informed the patient of the unlicensed use and its associated risk.

Please read the most up-to-date version of the Summary of Product Characteristics on the electronic medicines compendium (eMC) before prescribing valproate.

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.

- Refer any new patients 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 is complying with **prevent**. i.e. ensure that:
  - She has the Patient Guide and has a copy of her Annual Risk Acknowledgment Form signed by the specialist, and file a copy of the 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.
  - Tell her to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant.
- Remind all female patients that they will need to see their specialist at least once every year while taking valproate medicines.

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.

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 of **prevent** – the valproate pregnancy prevention programme are fulfilled.

- For new patients, only start treatment with valproate 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 that you invite all women on **prevent** for an annual review. 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 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 initiation and every annual visit); give a copy to her and send one to her GP.
- Refer for contraception services as needed.

Women of childbearing potential planning to become pregnant

- Ensure she understands the risks of valproate in pregnancy.
- Switch valproate to another therapeutic option. The conditions of **prevent** continue to apply until the switch from valproate is complete.
- 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.

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.

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 is not aware of the need for contraception and has not been seen by her GP/Specialist in the past year, dispense their medicine and 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 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.

The conditions of **prevent** continue to apply until the switch from valproate is complete.

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

General considerations for patients with bipolar disorder:

"If mood stabilizers are to be withdrawn, it is recommended that the dose be tapered down slowly as this reduces the risk of relapse."[2]

"Therefore valproate is to be discontinued gradually over few weeks to reduce early recurrence. In the case of an acute manic episode in a pregnant woman taking valproate, a much faster cross tapering while installing the alternative is recommended."[3]

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.

The conditions of **prevent** continue to apply until the switch from valproate is complete.

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%.[4] Available data show that the risk is dose-dependent. The risk is greatest at higher doses (above 1 g 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[5–8] 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.[9] 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.[10]

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).[11]

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For further copies of this information booklet please contact Sanofi medical information department on

0845 372 7101

or email

UK-Medicalinformation@sanofi.com

Information about valproate use can also be found online at www.medicines.org.uk. Enter "valproate" in the search box and then click on "Risk Materials" next to any of the medicines that appear.

Adverse event reporting

▼ This medicinal product is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/**

Adverse events should also be reported to the Sanofi drug safety department on **0800 090 2314**, or to the relevant manufacturer of the product if not Sanofi.

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