UPDATED DECEMBER 2023

Guide for Healthcare Professionals

Information on the risks of Valproate use in all patients

This medicine will be referred to as valproate throughout this guide and covers the brands Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil.

prevent
valproate pregnancy prevention programme

Read this guide carefully before prescribing valproate to patients.

- It is a part of **prevent** – **the valproate Pregnancy Prevention Programme**, aimed at minimising pregnancy exposure during treatment with valproate. (This programme will be referred to as **prevent** throughout this guide).
- It also includes information on the risks of valproate for male patients.

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 patient's pregnancy.

Medicines & Healthcare products Regulatory Agency

The information in this guide has been approved by the Medicine and Healthcare products Regulatory Agency (MHRA).

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PURPOSE OF THIS GUIDE

This guide provides up-to-date information about

- The risks of:
  - **Congenital malformations and neuro-developmental disorders** in children of mothers exposed to valproate during pregnancy.
  - **Male infertility**
  - **Testicular toxicity in animals**
- Conditions of valproate prescribing in epilepsy and bipolar disorder
- Key points for patient discussions

The risks of valproate 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.

Healthcare professionals (HCPs) targeted by this guide include, but are not limited to:

- Specialist prescribers
- General Practitioners
- Gynaecologists/obstetricians, Midwives, Nurses
- Pharmacists

The valproate educational materials developed for all patients treated with valproate include the following documents:

- Guide for Healthcare Professionals
- Patient Guide
- Annual Risk Acknowledgment Form for female patients
- Risk Acknowledgement Form for male patients starting valproate
- Pharmacy Poster (female patients)
- Pharmacy Warning Stickers
- Patient Card (female patients)

What's new in this Guide?

The main changes made from the previous version (dated November 2021) are as follows:

New patients:

- New requirement for prescribers: for patients aged under 55 years, two specialists must independently consider and document that there is no other effective or tolerated treatment when initiating patients on valproate.

Females:

- New requirement for prescribers: for female patients aged under 55 years taking valproate, two specialists must independently consider and document that there is no other effective or tolerated treatment at their next annual review.
- New information: the risk of eye malformations for exposed pregnancies.
- Updated information: the risk of valproate use in polytherapy during pregnancy.

Males:

- New information: the risks associated with use of valproate in male patients.

1. Treatment of female patients with valproate a. prevent – the valproate Pregnancy Prevention Programme

Valproate is an effective treatment for epilepsy and bipolar disorder.

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations (11%) and neurodevelopmental disorders (up to 30-40%) which may lead to permanent disability.

Valproate should not be used in female patients aged under 55 years, unless two specialists experienced in the management of epilepsy or bipolar disorder independently consider and document that there is no other effective or tolerated treatment.

The countersigning specialist must document their decision according to local arrangements. Discussion of cases at multidisciplinary team (MDT) meetings can substitute for the second signature, through a named representative of the MDT who must be a specialist prescriber.

Valproate in any indication must be prescribed and dispensed according to **prevent** (refer to section 4.4 of the Summary of Product Characteristics (SmPC) for further details).

- Conditions of valproate prescribing in epilepsy and bipolar disorder

	Epilepsy	**Bipolar disorder**
Female Patients aged **under 55 years**	- Valproate must NOT be prescribed unless: Two specialists independently consider and document that there is no other effective or tolerated treatment. AND The conditions of **prevent** are fulfilled (as applicable, for female patients of childbearing potential).	
In **pregnancy**	Valproate must NOT be prescribed unless: Two specialists independently consider and document that there is no other effective or tolerated treatment.	Valproate must NOT be prescribed.

- The conditions of **prevent** need to be maintained during the entire duration of treatment with valproate. This includes patients who are switching to a therapy other than valproate – the conditions of **prevent** should be continued until valproate is discontinued.
- Treatment with valproate must be reviewed regularly and at least annually.
- Please read the most up-to-date version of the SmPC on the electronic medicines compendium (eMC) (www.medicines.org.uk) before prescribing valproate.

Contraception

Female patients 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 highly effective 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 with the patient, involving the patient in the discussion to support her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

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**. Women aged under 55 years should have their treatment reviewed by two specialists. Once the clinical decision to prescribe valproate has been independently considered and documented by two specialists, the patient's subsequent annual reviews do not require the countersigning specialist, unless the patient's circumstances have changed.

The only exception to **prevent** is when the specialist prescriber considers that there are reasons to indicate that there is no risk of pregnancy:

- The absence of risk of pregnancy is permanent (e.g., post-menopausal patients or those after hysterectomy).
- The absence of risk may change (e.g., the patient is pre-menarche). Although **prevent** does not apply to these patients, their treatment with valproate must be reviewed regularly and at least annually.

Female children receiving valproate who have not yet reached menarche DO NOT need to fulfil the conditions of **prevent**, but they and their responsible person (parent/caregivers) need to be aware of the importance of the risks relating to exposure to valproate during pregnancy.

Also, the patient or responsible person must be asked to contact their General Practitioner (GP) once the patient using valproate experiences their first period (menarche). Their GP will refer the patient back to the specialist.

The reasons why **prevent** does not apply to the patient should be documented on the Annual Risk Acknowledgment Form. The patient or responsible person should sign the Annual Risk Acknowledgment Form to confirm that **prevent** does not currently apply to this patient and that risks have been discussed.

b. Actions for HCPs

Actions for General Practitioners

Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of **prevent** are fulfilled.

- Refer any new patient to a specialist prescriber for diagnosis and initiation of treatment.
- Arrange to see each female patient after specialist review and, if on valproate, ensure the patient is complying with **prevent** (where applicable) i.e., ensure that:
  - The patient has the Patient Guide and a copy of the signed Annual Risk Acknowledgment Form is filed in the patient's medical records.
  - The patient is using effective contraception and understands the need to comply with effective contraception throughout treatment with valproate and undergo pregnancy testing when required e.g., if there is any reason to suggest lack of compliance or lack of effectiveness of contraception.
  - Remind the patient to contact you immediately if they suspect there has been a problem with their contraception or if they may be pregnant.
  - In case of female children using valproate, remind the patient's responsible person to contact their GP once the patient using valproate experiences their first period (menarche). Their GP will refer the patient back to the specialist.
- Remind all female patients that they will need to see their specialist prescriber at least annually whilst taking valproate and arrange the referral annually as required.

Female patients who are planning to become pregnant.

- Inform the patient not to stop contraception or valproate until told to by their specialist prescriber.
- Refer the patient to their specialist prescriber who is managing their condition.

Female patients who are pregnant

- Inform the patient not to stop valproate and explain the reasons (e.g., their condition may become worse).
- Refer the patient to their specialist prescriber and ask for them to be seen urgently (within days).

Actions for specialist prescribers

Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of **prevent** are fulfilled.

Female patients not planning to become pregnant.

- For new female patients aged under 55 years, only start treatment with valproate if:
  - You and another specialist (countersigning specialist) independently consider and document that there is no other effective or tolerated treatment.

    - Discussion of cases at multidisciplinary team (MDT) meetings can substitute for the second signature, through a named representative of the MDT who must be a specialist prescriber.
  - Pregnancy is excluded by means of a negative pregnancy test.
- Assess the potential for pregnancy in all female patients and if necessary, discuss the need for the patient to fulfil the conditions of the **prevent** programme if they are to take valproate.
- Where possible, existing patients should be switched to another treatment and for those continuing to receive valproate the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually.
- Ensure the patient understands the risks to an unborn baby exposed to valproate *in utero* and provide them the Patient Guide.
- Ensure the patient understands the need to comply with effective contraception throughout treatment and undergo pregnancy testing when required – e.g., if there is any reason to suggest lack of compliance or lack of effectiveness of contraception.
- Ensure that you invite all female patients on valproate for an annual review. Continue treatment with valproate only if there is no other effective or tolerated treatment.
- Two specialists (specialist prescriber and countersigning specialist) must complete and sign the Annual Risk Acknowledgment Form:
  - for new patients at initiation of valproate treatment.
  - for existing patients, only at their next annual review, unless their circumstances change.
- For subsequent annual reviews, only the prescribing specialist must complete and sign the Annual Risk Acknowledgement Form. The completed form should be stored in the patient's medical notes and shared with the patient and, if applicable, any healthcare professionals named on the form.
- Refer for contraception advice as needed.
- For female children receiving valproate, the importance of risks relating to pregnancy exposure to valproate should be discussed well before menarche and patients should be switched to another treatment unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk associated with exposure during pregnancy is not applicable.

Female patients planning to become pregnant

- Ensure the patient understands the risks of taking valproate during pregnancy.
- Switch valproate to another therapeutic option. The conditions of **prevent** continue to apply until the switch from valproate is complete.
- Remind the female patient not to stop contraception until the switch is achieved and they are no longer taking valproate.
- If switching is not possible, refer the patient for counselling about the risks of valproate to an unborn baby during pregnancy.

Female patients who are pregnant

- Female patients who are pregnant should have their treatment switched to another treatment whenever possible.
- Female patients with epilepsy who have to continue treatment in pregnancy (i.e., if two specialists independently consider and agree that switching to another treatment is not possible) should be referred to a specialist experienced in prenatal medicine for appropriate monitoring.

Actions for Pharmacists

- Ensure the Patient Card is provided every time valproate is dispensed to a female patient.
- Ensure the patient has received the Patient Guide or knows they can access it online using the QR code on the package leaflet.
- Confirm with female patients that they have been made aware of the risks in pregnancy.
- Confirm with female patients that they have been made aware to always use effective contraception and to see their General Practitioner (GP) to be urgently referred to their specialist, should they be planning a pregnancy.
- Confirm with female patients that they have been made aware to NOT TO STOP valproate and to immediately contact their GP for an urgent referral to their specialist in case of suspected pregnancy.
- Dispense valproate in the original package. In exceptional circumstances, where a patient needs to receive their medication in different packaging such as a Monitored Dosage System, ALWAYS provide a copy of the package leaflet, the patient card and add a valproate warning sticker to the outer box.
- If a female patient reports that:
  - They are not continuously taking an effective method of contraception,
  - They are not aware of the need for contraception or
  - They have not been seen by their specialist in the past year,

  dispense their medicine and refer them to their GP (contact the GP if necessary).

Actions for Gynaecologists/obstetricians, Midwives and Nurses

- Provide counselling on methods of contraception and pregnancy planning.
- Provide information about the risks of using valproate during pregnancy.
- When a patient consults for pregnancy, urgently refer the patient to be seen (within days) by their specialist prescriber and to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

c. Switching or discontinuing valproate

Patients with epilepsy

Valproate is contraindicated in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment.

Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of **prevent** are fulfilled.

If a female patient has not yet experienced menarche, a specialist prescriber experienced in the management of epilepsy must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate other treatment before and/or at the time of first period.

If a female patient is planning to become pregnant, a specialist prescriber experienced in the management of epilepsy must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate other treatment before contraception is discontinued and prior to conception.

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

If a female patient becomes pregnant whilst taking valproate, they must be immediately referred to a specialist prescriber to consider other 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 from valproate to another treatment will commonly occur over at least 2–3 months. The new medication is usually first gradually introduced as an 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 other treatment options, in exceptional circumstances a pregnant female patient must receive valproate for epilepsy as agreed by two independent specialists:

- There is no dose threshold considered to be without any risk. However, the risk of birth defects and neuro-developmental disorders is higher at higher doses. This includes when valproate is used in combination with other medicines to treat epilepsy.
- 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.

Patients with bipolar disorder

Valproate is contraindicated in pregnancy.

Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of **prevent** are fulfilled.

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

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

If a female patient becomes pregnant, they must be immediately referred to a specialist prescriber and the patient must be switched 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.[1]

Therefore, valproate should be discontinued gradually over a few weeks to reduce the risk of relapse. In the case of an acute manic episode in unplanned pregnancy in a woman taking valproate, a much faster cross tapering while up titrating another treatment is recommended.[2]

d. Information on congenital malformations and on neuro-developmental disorders

Valproate has known teratogenic effects which may result in congenital malformations and neuro-developmental disorders which may lead to permanent disability.

Congenital malformations

A meta-analysis (including registries and cohort studies) showed that approximately 11%[3] of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 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.

Available data show an increased incidence of minor and major malformations. 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.[4]
- 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 common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Neuro-developmental 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 neuro-developmental disorders which may lead to permanent disability (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 neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.

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[5-8] in children exposed *in utero* to valproate show that up to 30–40% 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 children (age 6) with a history of valproate exposure *in utero* was on average 7–10 points lower than those children exposed to other antiepileptics during pregnancy[9], although the role of confounding factors related to intellectual disability cannot be excluded. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There is limited data on the long-term outcomes.

Available data from a population-based study show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (an approximately 3-fold) and childhood autism (an approximately 5-fold) compared to the unexposed population in the study.[10]

Available data from another population-based study show that children exposed to valproate *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.[11]

2. Treatment of male patients with valproate

Valproate should not be initiated in male patients aged under 55 years, unless two specialists experienced in the management of epilepsy or bipolar disorder independently consider and document that other treatments are not effective or tolerated or the risk of infertility or potential risk of testicular toxicity are not applicable.

a. Information on male infertility and testicular toxicity in animals

Male infertility

Valproate administration may impair fertility in men. Fertility dysfunctions are in some cases reversible, at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

The risk of infertility should be discussed with all male patients.

Testicular toxicity in animals

Toxicity studies in animals exposed to valproate have shown testicular degeneration/atrophy, spermatogenesis abnormalities and decrease in testes weight in adult rats. Testicular atrophy and decrease in testes weight have been observed in juvenile animal populations.

The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

b. Actions for HCPs

Actions for General Practitioners

No new action required by GPs for any male patient aged under 55 years, as two specialists are required to independently consider and document that there is no other effective or tolerated treatment.

Refer any new patient to a specialist prescriber for diagnosis and to initiate treatment if appropriate.

Actions for Specialist prescribers

- No new male patients aged under 55 years should be initiated on valproate, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the risk of infertility or potential risk of testicular toxicity are not applicable.
- If a new male patient has a permanent reason that these risks do not apply (e.g., vasectomy or infertility due to other causes), the countersigning specialist is not required, and the specialist prescriber should record the reason in the relevant section of Risk Acknowledgement Form for male patients and in their medical notes.
- Ensure male patients on valproate have the Patient Guide or know they can access it online using the QR code on the package leaflet.
- A Risk Acknowledgement Form for Males needs to be discussed and completed with the patient at time of treatment initiation.
- Ensure the patient is made aware of the risk of male infertility and testicular toxicity in animals associated with valproate therapy.
- For male children receiving valproate, their responsible person should be made aware of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance.

Actions for Pharmacists

- Ensure the patient has received the Patient Guide or knows they can access it online using the QR code on the package leaflet.
- Dispense valproate in the original packaging. In exceptional circumstances where a patient needs to receive their medication in different packaging such as a Monitored Dosage System ALWAYS provide a copy of the package leaflet.

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For further copies of this guide please contact Sanofi Medical Information department on

0800 035 2525

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. This will allow quick identification of new safety information.

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme, via the Yellow Card website www.mhra.gov.uk/yellowcard, the free Yellow Card app available in Apple App Store or Google Play Store, and also some clinical IT systems for healthcare professionals. Alternatively, you can call 08007316789 for free, Monday to Friday between 9am and 5pm.

By reporting adverse drug reactions, you can help provide more information on the safety of this medicine.

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