VALPROATE GUIDE

FOR HEALTHCARE PROFESSIONALS

Information on the risks of valproate use in all patients.

prevent
valproate pregnancy prevention programme

Read this guide carefully before prescribing or dispensing 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.

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.

Medicines & Healthcare products Regulatory Agency

CONTENTS

BD: Bipolar Disorder; **HCP:** Healthcare Professional; **NDD:** Neurodevelopmental Disorders; **WCBP:** Women of Childbearing Potential

Purpose of this Healthcare Professional guide

Valproate educational materials have been developed for all patients treated with valproate and include the following documents:

- This HCP Guide
- 2 Patient Guides (one each for female and male patients)
- Patient Card
- Annual Risk Acknowledgement Form for female patients
- Risk Acknowledgement Form for male patients starting valproate
- Pharmacy Poster

The objective of this HCP guide is to provide all HCPs involved in the patient journey with information about:

- The prescribing conditions in epilepsy and bipolar disorder
- The risks of:
  - Congenital malformations, neuro-developmental disorders and lower weight at birth for the gestational age in children of mothers exposed to valproate during pregnancy.
  - Potential neurodevelopmental risk to children born to men treated with valproate in the 3 months before conception
  - Male infertility
  - Testicular toxicity in animals
- The actions necessary to minimise the risks
- 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.

HCPs targeted by this guide include, but are not limited to:

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

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.

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

What's new in this Guide?

- Updated for male risks
    - Potential neurodevelopmental risk to children born to men treated with valproate in the 3 months before conception
- Updated for female risks
    - Lower weight at birth for the gestational age associated with the use of valproate during pregnancy

1 What you must know/do about the conditions of valproate prescription in female patients

- 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.** Children of mothers exposed to valproate during pregnancy may also experience lower weight at birth for the gestational age.
- 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.
- In any indication, valproate must be prescribed and dispensed according to the conditions of the **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.

2 What is your role?

Specialist Prescriber

General Practitioner

Gynaecologist/Obstetrician/ Nurse/ Midwife

Pharmacist

What is your role?
Specialist Prescriber

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.

INITIAL valproate prescription for patients aged under 55 years

Pregnancy is excluded by means of a negative pregnancy test.

Complete and sign the Annual Risk Acknowledgment Form with another specialist (countersigning specialist).

Existing female patients taking valproate

NOT PLANNING a pregnancy

Where possible, existing patients should be switched to another treatment. Complete and sign the Annual Risk Acknowledgment Form. A countersigning specialist is required at one annual review, unless the patient's circumstances have changed.

Explain/remind and ensure patient's understanding of

I. The risks of congenital malformations, neurodevelopmental disorders and lower weight at birth for the gestational age for children exposed in utero.

II. The need to:

- Comply with **effective contraception throughout treatment - refer for contraception advice** as needed.
- Undergo **pregnancy testing** when required during treatment e.g., if there is any reason to suggest lack of compliance or lack of effectiveness of contraception.
- **Reassess** treatment with you at least **annually**. Continue treatment with valproate only if there is no other effective or tolerated treatment.

Complete and sign the Annual Risk Acknowledgement Form at initiation and at each annual visit (for those continuing to receive valproate). 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.

Specifically for female children

I. 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.

⚠ Explain that if the patient thinks they are pregnant or becomes pregnant, **they should not stop valproate and should contact their GP immediately to be referred to you.**

Existing female patients taking valproate

PLANNING pregnancy

Explain that contraception should only be stopped after complete valproate cessation.

Patients who are pregnant

Their treatment should be 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.

I. **Ensure the patient understands the risks** of taking valproate during pregnancy.

II. **Switch valproate** to another therapeutic option. The conditions of prevent continue to apply until the switch from valproate is complete.

III. Remind the female patient not to stop contraception until the switch is achieved and they are no longer taking valproate.

IV. If switching is not possible, refer the patient for counselling about the risks of valproate to an unborn baby during pregnancy.

⚠

- Two specialists (specialist prescriber and countersigning specialist) must complete and sign the Annual Risk Acknowledgement Form:
  - For new patients at initiation of valproate treatment.
  - For existing patients, only once at an annual review, unless their circumstances change.
- For subsequent annual reviews, only the prescribing specialist must complete and sign the Annual Risk Acknowledgement Form. The date the countersigning specialist originally signed the ARAF should be carried forward within step 2, unless the patient's circumstances have changed. 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.

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 THE PATIENT IS...

INITIATING VALPROATE

You need to

I. Refer to a **specialist prescriber** for diagnosis and initiation of treatment.

II. 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 Acknowledgement 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 that they will need to see their specialist prescriber at least annually whilst taking valproate and arrange the referral annually as required.

Specifically for female children

I. Remind the patients' responsible person to contact you once the patient using valproate experiences their first period (menarche). You will refer the patient back to their specialist.

Remind the patient to contact you immediately if they suspect there has been a problem with their contraception or if they may be pregnant.

IF THE PATIENT IS...

PLANNING pregnancy

Inform the patient not to stop contraception or valproate until told to by their specialist prescriber.

PREGNANT

Inform the patient not to stop valproate and explain the reasons (e.g. their condition may become worse).

I. Refer the patient promptly to their specialist prescriber for switching to alternative treatment if suitable

II. Tell your patient to continue valproate.

Provide the Patient Guide

Actions

I. Provide counselling on methods of contraception and pregnancy planning
   - Provide information about the risks of using valproate during pregnancy

II. 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.

Provide the Patient Guide

In epilepsy, valproate is contraindicated during pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment.

In bipolar disorder, valproate is contraindicated during pregnancy.

Explain that if the patient thinks they are pregnant, or becomes pregnant, **they must not stop valproate and must contact their specialist immediately.**

Confirm with patients that

I. They have been made aware of the risks in pregnancy

II. 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.

III. 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.

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).

In epilepsy, valproate is contraindicated during pregnancy unless there is no suitable alternative.

In bipolar disorder, valproate is contraindicated during pregnancy.

About educational materials

PATIENT CARD

- Ensure it is provided to patients
- Discuss it every time valproate is dispensed
- Advise the patient to keep it on them at anytime

PATIENT GUIDE

- Ensure the patient received it

ONLINE INFORMATION

- Remind the patient that online information can also be found by scanning the **QR code (on the package leaflet)**

- Display the pharmacy poster at a visible place in the dispensary
- 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 and the patient card.

3 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 stabilisers are to be withdrawn, it is recommended that the dose be tapered down slowly as this reduces the risk of relapse.

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.

4 What are the valproate risks if taken during pregnancy?

Valproate use during pregnancy is harmful for the unborn child and may lead to permanent disability. Children exposed in utero to valproate have a high risk for:

- Congenital malformations
- Neurodevelopmental disorders
- Lower weight at birth for the gestational age

1. Congenital malformations

About 11%[3] of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations.

This risk is greater than 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.

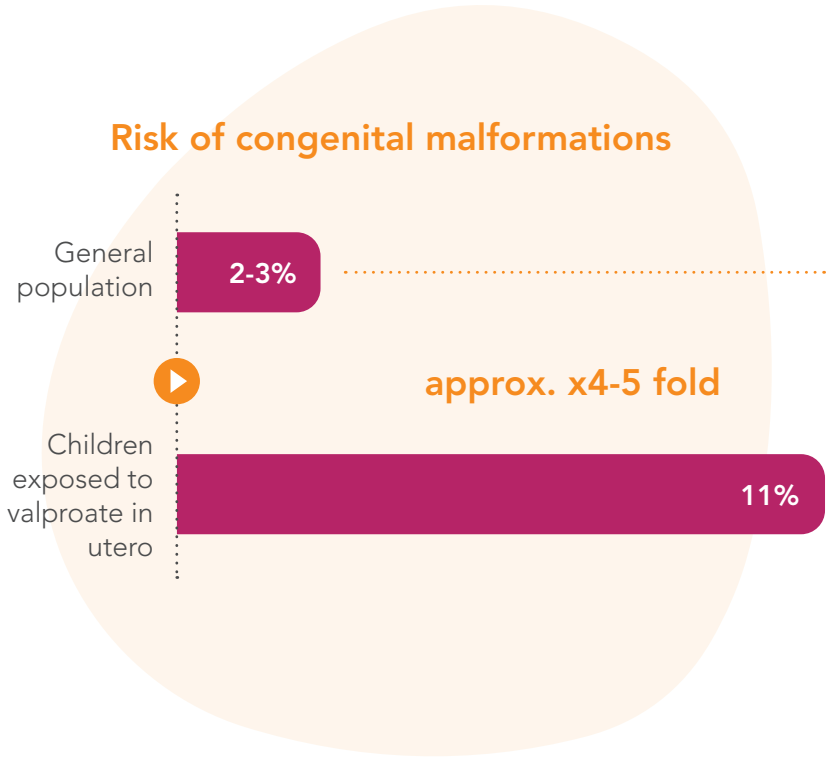
Available data show an increased incidence of minor or major malformations. The most common types of malformations included:

- Neural tube defects
- Facial dysmorphism
- Cleft lip and palate
- Craniostenosis
- Cardiac, renal and urogenital defects
- Limb defects (including bilateral aplasia of the radius)
- 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.



2. Neurodevelopmental disorders

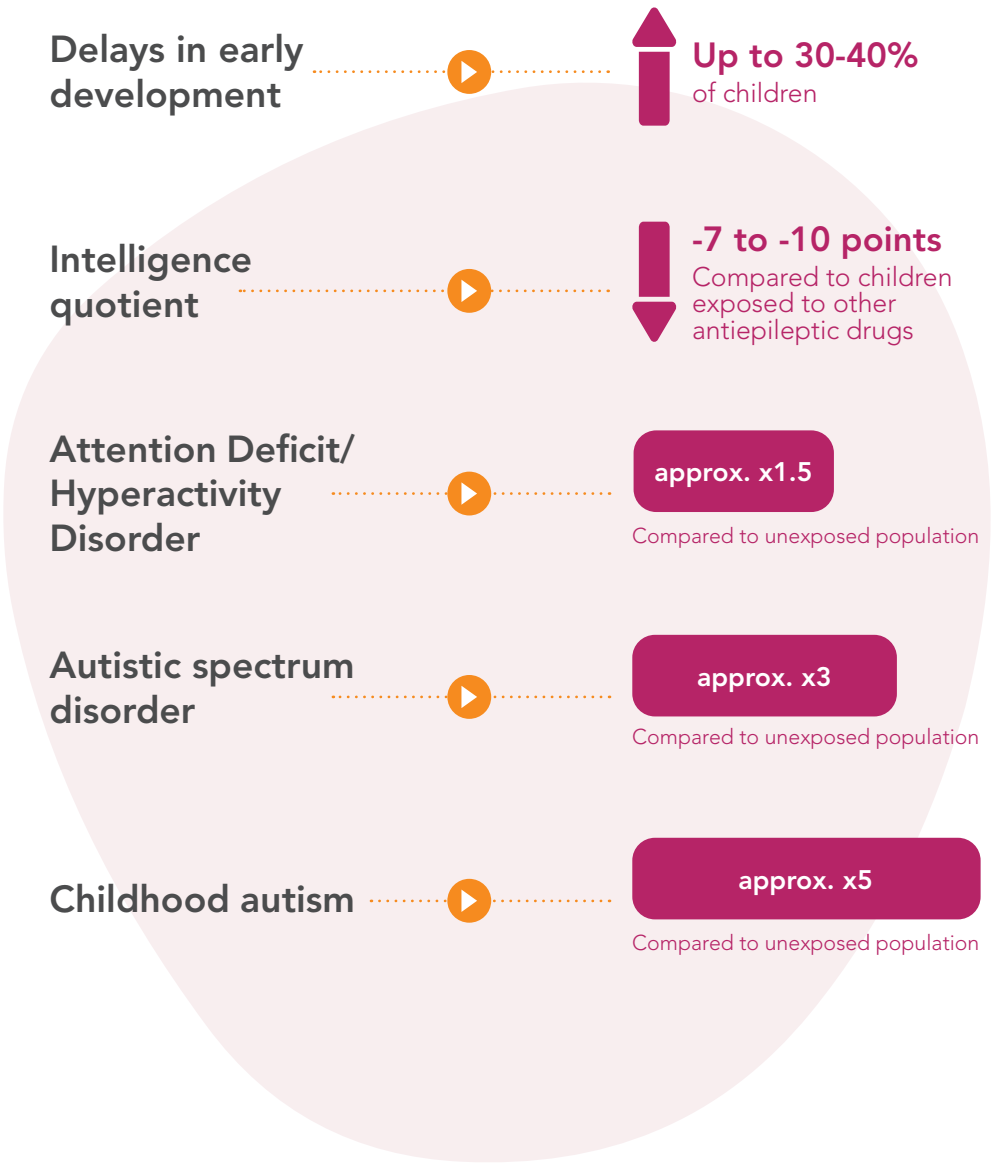
- Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children.
- The risk of neuro-developmental disorders which may lead to permanent disability (including that of autism) seems to be dose dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data.
- 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 polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopmental 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.
- When valproate is administered in monotherapy, studies in children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as:[6-9]
    - Talking and walking later
    - Lower intellectual abilities
    - Poor language skills (speaking and understanding)
    - Memory problems
- In children (age 6) with a history of valproate exposure in utero, intelligence quotient measured was on average 7-10 points lower than in children exposed to other antiepileptics during pregnancy[10], 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 are limited data on the long-term outcomes.
- There is an increased risk of the following in children with a history of valproate exposure in utero compared to the unexposed population:
    - Attention deficit/hyperactivity disorder[11]: approximately 1.5-fold
    - Autistic spectrum disorder[12]: approximately 3-fold
    - Childhood autism[12]: approximately 5-fold

3. Lower weight at birth for the gestational age

Epidemiological studies[13-16] have reported a decrease in mean birth weight, and higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate in utero in comparison to unexposed or lamotrigine-exposed children.

Available data in humans do not allow for a conclusion on a potential dose-related effect.

Risks increased in children exposed to valproate in utero



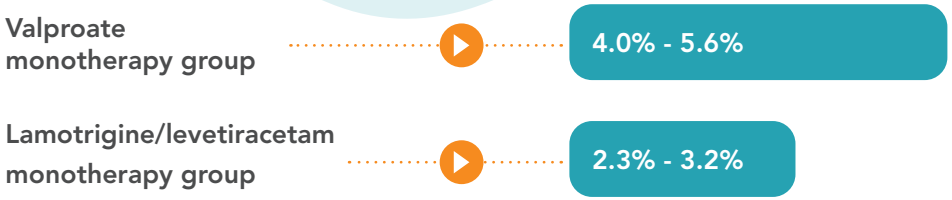
1 What you must know about the risks for male patients treated with valproate

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. Potential risk to children born to men treated with valproate in the 3 months before conception.

A retrospective observational study in 3 European Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to male patients treated with valproate as monotherapy in the 3 months prior to conception compared to those born to male patients treated with lamotrigine or levetiracetam as monotherapy.

Comparison of adjusted cumulative risk of NDDs in children born to male patients treated with valproate in the 3 months prior to conception vs children born to male patients treated with lamotrigine or levetiracetam.



The pooled adjusted hazard ratio for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% Confidence Interval: 1.09, 2.07).

The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

b. 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.

2 What is your role?

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, of the potential risk to children born to men treated with valproate in the 3 months before conception and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance.

It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.

SPECIALIST PRESCRIBERS

Explain/remind and ensure patient's knowledge of

I. **The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception.**

II. The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception.

III. As a precautionary measure, discuss with the patient regularly **the need**:
   - To consider **effective contraception**, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation.
   - To consult a specialist **to discuss treatment alternatives** when they are planning to conceive a child and before discontinuation of contraception.

IV. Male patients **should not donate sperm** during treatment or for at least 3 months after the treatment discontinuation.

For male patients planning to conceive a child, other suitable treatment options should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.

It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Male patients treated with valproate should be regularly reviewed by their GP or specialist.

Provide the Patient Guide

PHARMACIST

- Ensure the patient 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.

REFERENCES

1. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand J. Psychiatry 2015, Vol. 49(12):1-185.
2. Minutes and answers from the SAG Psychiatry meeting on Valproate-EMA/679681/2017.
3. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.
4. 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;113:192-7.
5. Jentink J, Bakker MK, Nijenhuis CM, Wilffert B, de Jong-van den Berg LT. Does folic acid use decrease the risk for spina bifida after in utero exposure to valproic acid? Pharmacoepidemiol Drug Saf. 2010 Aug;19(8):803-7.
6. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October; 51(10):2058-65.
7. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647.
8. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009; 360 (16):1597-1605.
9. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236.
10. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar; 12(3):244-52.
11. 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.
12. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013; 309(16):1696-1703.
13. Kilic D, Pedersen H, Kjaersgaard MI, Parner ET, Vestergaard M, Sørensen MJ et al. Birth outcomes after prenatal exposure to antiepileptic drugs--a population-based study. Epilepsia. 2014 Nov;55(11):1714-21.
14. Hernández-Díaz S, McElrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB; North American Antiepileptic Drug Pregnancy Registry. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017 Sep;82(3):457-65.
15. Margulis AV, Hernandez-Diaz S, McElrath T, Rothman KJ, Plana E, Almqvist C et al. Relation of in-utero exposure to antiepileptic drugs to pregnancy duration and size at birth. PLoS One. 2019 Aug 5;14(8):1-21.
16. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate : evidence of dose relationship in teratogenic effect. CNS Drugs. 2008;22(4):325-34.

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.

MAT-XU-2500597 (v1.0)

May 2025