

Information on the risks of valproate use in female patients and pregnant women.

Contraception and pregnancy prevention

Please read this booklet carefully before any prescription of valproate to female patients.

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

Information about valproate use can also be found on-line at Sanofi.com.au/valproate

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PURPOSE OF THIS GUIDE

This Guide for healthcare professionals (HCPs) is an informational tool, providing 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.

Valproate educational tools that are available for girls and women of childbearing potential treated with valproate include:

- The Patient Guide

Use this booklet together with the Patient Guide.

The Patient Guide is available electronically at Sanofi.com.au/valproate. Please ensure all your female patients treated with valproate - girls and women of child bearing potential (or their parents / legal guardian or caregiver for patients who are minors or without the capacity to make an informed decision) are aware of how to access the website.

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

Please read the most up-to-date version of the Australian Approved Product Information Sheet available at www.tga.gov.au, or New Zealand Data Sheet available at <http://www.medsafe.govt.nz> before prescribing valproate.

1. INFORMATION ON CONGENITAL MALFORMATIONS AND ON DEVELOPMENTAL DISORDERS

Valproate is an effective treatment for epilepsy or mania.

In female children 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 female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described below.

1. CONGENITAL MALFORMATIONS

Data derived from two meta-analysis (including registries and cohort studies) have shown that 10.73% (95% Confidence Interval: 8.16-13.29%)¹ to 10.93% (95% Confidence Interval: 8.91-13.13%)² of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations). This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%¹. 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.

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.

Studies³⁻⁶ in preschool children show that up to 30-40% of children with a history of valproate exposure *in utero* experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6 years old) with a history of valproate exposure *in utero* was on average 7-10 points lower than children exposed to other antiepileptic drugs⁷. 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) and childhood autism (an approximately five-fold) compared with the general study population⁸.

Limited data suggests that children with a history of valproate exposure *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)⁹.

3- CONDITIONS OF VALPROATE PRESCRIPTION

Before prescribing valproate to females of childbearing potential, the prescriber must ensure that:

- 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 minimize the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception*, without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options, if suitable, prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient is able to access the online information at sanofi.com.au/valproate
- The patient has verbally acknowledged that she has understood the hazards and necessary precautions

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.

* At least one effective method of contraception (preferably a 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 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 effective contraception.

4- TREATMENT OF FEMALE PATIENTS WITH VALPROATE

Valproate is an effective treatment for epilepsy and mania.

In female children and women of childbearing potential valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or mania disorder.

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

If, after medical evaluation, you are considering prescribing valproate to your female patient, either for the first time or a repeat prescription, you should:

- **Confirm that treatment with valproate is appropriate for your patient**
 - Individual circumstances should be evaluated on a case by case basis. If alternative treatments are ineffective not tolerated for your patient, ensure you have discussions with your patient (or her parents/ legal guardian / caregiver) regarding the risks when taking valproate when pregnant.
 - If your patient is a minor, or has limited mental capacity, all discussions and decisions regarding treatment should be had with her parents / legal guardian / caregiver, in conjunction with your patient (where appropriate).
- **Explain and make sure your patient and/or her parents / legal guardian / caregiver have understood the following:**
 - The patient needs to undergo a plasma pregnancy testing **prior** to initiation of treatment and during treatment, as needed, to exclude pregnancy
 - The risks to pregnancy associated with the underlying condition
 - The specific risks related to valproate when used in a pregnancy. Direct them, or their parents / legal guardian /caregiver to where the Patient Guide is available online at sanofi.com.au/valproate.
 - The need to comply with an effective contraception, without interruption, during the entire duration of treatment with valproate to avoid an unplanned pregnancy. Refer your patient for contraception counselling, if needed.
 - *At least one effective method of contraception (preferably a 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 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 effective contraception.*
 - The need for regular (at least annual) review of the patient's treatment by a specialist
 - Advise patients that if they are planning to become pregnant, or do become pregnant, to contact you immediately. They should continue their valproate treatment until you advise them what to do.
- **Additional Recommendations when valproate is prescribed to female children:**
 - Assess the most appropriate time to give advice on contraception and prevention of pregnancy (Refer your patient to a specialist for counselling if needed)
 - Explain to the parents / legal guardian / caregiver (and to the child depending on her

age) the importance of contacting a specialist as soon as the female child treated with valproate experiences menarche

- Reassess the need for valproate therapy at least annually and consider alternative treatment options in female children who have experienced menarche
- Assess all options to switch female children to alternative treatment before they reach adulthood.

Pharmacists at time of Dispensing

- Show the female patient (or their parent / legal guardian / caregiver) where the QR code and web address are located on the packaging to access the online Patient Guide. Ensure they are able to access the information.
- Reinforce the need to comply with an effective method of contraception, without interruption, during the entire duration of treatment with valproate
- Remind the patient (or their parent/legal guardian/caregiver) to contact their doctor immediately not to stop the treatment with valproate and to immediately contact their doctor when planning a pregnancy or in case of a suspected pregnancy
- Dispense Valproate in the original package with an outer warning regarding use in pregnancy.
- *For New Zealand – Where possible, the original packaging should be retained and provided to female patients

C. WOMAN OF CHILDBEARING POTENTIAL WHO ARE PLANNING PREGNANCY

1. Remind and make sure your patient understands the risks of birth defects and developmental disorders

- Inform your patient that these can be seriously debilitating when taking valproate during pregnancy
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure¹⁰
- Also inform your patient them about the risks of untreated seizures or bipolar disorder.

2. Switch and discontinue valproate to other therapeutic alternative if suitable:

- Read section 5 in this Guide on switching or discontinuing valproate
- Tell your patient to not stop contraception until the switch is achieved
- General Practitioners should refer their patient to the specialist for switching and discontinuation.

3. Refer your patient to a specialist for preconception counselling.

4. Instruct your patient to consult their family doctor and specialist as soon as she suspects or confirms she is pregnant.

- This is to start appropriate pregnancy monitoring
- This includes prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations
- When a patient consults for pregnancy refer the patient and her partner to a specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy.
- Direct them, or their parents / legal guardian /caregiver to where the Patient Guide is available online at sanofi.com.au/valproate.

5. Pharmacists, at time of dispensing

- Show the patient where the QR code and web address are located on the packaging to access the online Patient Guide. Ensure the patient is able to access them.
- Advise patients not to stop valproate medication unless their doctor has instructed them to and started an alternative medication.
- Remind patients (or her parents/legal guardian/caregiver) to not stop their contraception, unless their doctor has instructed them to.
- Remind patients to immediately contact their specialist when they suspect/are pregnant.
- If specialist has prescribed valproate, dispense it in the original packaging, with the pregnancy warning.
- *For New Zealand – Where possible, the original packaging should be retained and provided to female patients

7. For the specialist:

- Confirm that the patient or her parents / legal guardian / caregiver are aware of and fully understand the risks and recommendations associated with the use of valproate during pregnancy.

D. WOMAN WITH AN UNPLANNED PREGNANCY

- 1. Arrange an urgent consultation with your patient to reassess her treatment as soon as possible. Explain why she should continue her treatment until you have seen her.**
 - Review the risks regarding her condition for stopping her valproate medication, unless you are able to give other advice based on your assessment of the situation.
- 2. Switch and discontinue to other therapeutic alternatives if suitable**
 - Read section 5 in this Guide on switching or discontinuing valproate.
- 3. Make sure that your patient:**
 - Has fully understood the risks related to valproate and pregnancy.
 - Suggest further counselling if required.
- 4. Start specialised prenatal monitoring**
 - This is to start appropriate pregnancy monitoring
 - This includes prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations
 - Patient and her partner should be referred to a specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy
- 5. General Practitioners should refer their patient to the specialist for switching and discontinuation**

5. SWITCHING OR DISCONTINUING VALPROATE

Patients using Valproate for the Treatment of Mania

Valproate is contraindicated in pregnancy.

Valproate is contraindicated in women of childbearing potential unless the physician has provided information on the potential effects of valproate during pregnancy.

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

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

General considerations for bipolar disorder patients:

“If mood stabilizers are to be withdrawn, it is recommended that the dose be tapered down slowly as this reduces the risk of relapse.”¹¹

“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.”¹²

Patients using Valproate for the Treatment of Epilepsy

Valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.

Valproate is contraindicated in women of childbearing potential unless the risks associated with valproate during pregnancy have been discussed and understood.

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 epileptic patients:

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 (or a woman planning to become pregnant) 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 pre-natal medicine *for evaluation and counselling regarding the exposed pregnancy.*

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