

**VALPROATE
GUIDE**

FOR HEALTHCARE PROFESSIONALS
.....
**who manage girls and women
of childbearing potential
and male patients
treated with valproate***

**Includes information on use
of valproate in accordance
with the pregnancy
prevention program**

**YOU MUST READ THIS GUIDE CAREFULLY BEFORE
ANY PRESCRIPTION OF VALPROATE TO GIRLS (OF ANY AGE),
WOMEN OF CHILDBEARING POTENTIAL AND MALE PATIENTS**

.....

* Valproate is a generic term including valproic acid, valproate sodium, valproate semisodium, valproate

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Specialist
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Purpose of this Healthcare Professional guide

Valproate use during pregnancy is harmful for the unborn child. Children exposed in utero to valproate have a higher risk for:

- Congenital malformations,
- Neurodevelopmental disorders.

There is a potential risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception.

Valproate educational tools have been developed specifically for HCPs, female and male patients. They include:

- This HCP Guide
- An Annual Risk Acknowledgement Form (only for female patients)
- 2 different Patient Guides (for female and male patients)
- A Patient Card

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

- The prescribing conditions in girls, WCBP and male patients,
- The teratogenic and neurodevelopmental risks, associated with the use of valproate during pregnancy,
- The potential neurodevelopmental risk, associated with the use of valproate in the 3 months prior to conception for male patients,
- The actions necessary to minimize the risks.

HCPs targeted by this guide include:

- Specialists,

For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal representative/caregiver and make sure they clearly understand it.

Please read the most up-to-date version of the Summary of Product Characteristics before prescribing valproate.

1

What you must know/do about the conditions of valproate prescription in female, girls and adolescents patients?

- Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy, bipolar disorder or migraine.
- It should not be used in female children/adolescents and WCBP unless other treatments are ineffective or not tolerated.
- It should be prescribed and dispensed according to the conditions of the valproate Pregnancy Prevention Program.

She suffers from		
	Epilepsy	Bipolar disorder or Migraine
She is of childbearing potential Epilepsy: from menarche to menopause BD: adult women Migraine: adult women	You must NOT prescribe valproate <u>unless</u> the conditions of the Pregnancy Prevention Program are fulfilled	
She is pregnant	You must NOT prescribe valproate <u>unless</u> there is no suitable alternative treatment	 You must NOT prescribe valproate

Overview of the Pregnancy Prevention Program Conditions (for details read the Summary of Product Characteristics)

- Assess patients for pregnancy potential,
- Explain the risks of congenital malformations and neurodevelopmental disorders,
- Perform a pregnancy test prior to initiation and during treatment, as needed,
- Counsel on the need for effective contraception throughout the treatment,
- Explain the need for pregnancy planning,
- Explain the need to urgently consult the physician in case of pregnancy,
- Review regularly (at least annually) the treatment by the specialist,
- Provide the Patient Guide,
- Complete the Annual Risk Acknowledgement Form with the patient at initiation and at annual review.

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.



What is your role?

What you must do if you are managing a girl/adolescent treated with valproate

- Explain to her or her parents/caregivers (depending on age) the risks of congenital malformations and neurodevelopmental disorders
- Explain to her or her parents/caregivers the importance of contacting the specialist once she experiences menarche
- Reassess the need for valproate therapy at least annually and consider alternative treatment options as soon as she experienced menarche
- Make efforts to switch her to alternative treatment before she reaches adulthood.

Specialist - Epilepsy

Specialist - Bipolar or Migraine

SPECIALISTS prescribing valproate to girls and women of childbearing potential suffering from EPILEPSY

INITIAL valproate prescription

Only if:

- other treatments are ineffective or not tolerated
- pregnancy test is negative (for WCBP)

RENEWAL of valproate

NOT PLANNING a pregnancy

Reassess treatment at least annually

Explain/remind and ensure patient's understanding of

- The risks of congenital malformations and neurodevelopmental disorders for children exposed in utero
- The mandatory use of **effective contraception** (preferably an intra-uterine device, or implant, or 2 complementary forms including a barrier method)
 - even if patient has amenorrhea
 - without interruption during the entire valproate treatment duration
 - regardless of sexual activity status
 - refer for contraception services as needed
- The need to:
 - undergo pregnancy testing when required during treatment
 - **plan** for pregnancy
 - **reassess** epilepsy treatment with you **annually**

Complete the Annual Risk Acknowledgement Form at initiation and at each annual visit
Provide the Patient Guide

Specifically for girls

- Explain the risks of congenital malformations and neurodevelopmental disorders to the parents/caregivers (and children depending on their age)
- Explain to the parents/caregivers (and children depending on their age) the importance of contacting the specialist once a female child using valproate experiences menarche
- Assess the most appropriate time to give advice on contraception
- Reassess the need for valproate therapy at least annually
- Make efforts to switch the female children to alternative treatment before they reach adulthood

Explain that if she thinks she is pregnant or becomes pregnant, **she should not stop valproate and contact you immediately.**

FOR ALL PATIENTS: complete the **Annual Risk Acknowledgement Form** (in 2 copies) at initiation and annually; provide and discuss the **patient guide**

prescription in women

PLANNING pregnancy

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

Explain that contraception should only be stopped after complete valproate cessation

UNPLANNED pregnancy

The patient should not stop valproate and consult you urgently

I. Inform the patient and her partner about the risks

- to the unborn child exposed to valproate in utero
- of untreated seizures during pregnancy

II. Explain the need to switch to alternative treatment if suitable, and that it takes time:

- the new medication is gradually introduced as add-on to valproate
 - up to 6 weeks to reach effective dose
- then gradually withdraw valproate over weeks and months
 - commonly 2-3 months

III. If a seizure occurs during valproate withdrawal, maintain the minimum required dose

Complete the Annual Risk Acknowledgement Form at initiation and at each annual visit
Provide the Patient Guide

If, in exceptional circumstances, a pregnant woman must receive valproate for epilepsy

Valproate should preferably be prescribed:

- as monotherapy
- at the lowest effective dose, with daily dose divided into several small doses
- as a prolonged release formulation



Refer your patient and her partner to:

- a gynecologist/obstetrician/midwife
- a specialist to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

SPECIALISTS prescribing valproate to women of childbearing potential suffering from **BIPOLAR DISORDER or MIGRAINE**

INITIAL valproate prescription

RENEWAL of valproate

prescription in women

PLANNING
pregnancy

UNPLANNED
pregnancy

In bipolar disorder and migraine, valproate is contraindicated during pregnancy

Switch to alternative treatment
prior to conception

The patient should not stop valproate
and consult you urgently

Inform the patient and her partner about the risks

- to the unborn child exposed to valproate in utero
- of untreated bipolar disorder or migraine during pregnancy

- Explain that contraception should only be stopped after complete valproate cessation
- Valproate should be discontinued gradually over few weeks to reduce early recurrence¹

- Discontinue valproate
- Switch to alternative treatment:
**a fast cross tapering while
installing the alternative
treatment is recommended²**

Refer your patient and her partner to:

- a gynecologist/obstetrician/midwife
- a specialist to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

Complete the Annual Risk Acknowledgement Form at initiation
and at each annual visit
Provide the Patient Guide

Explain/remind and ensure patient's understanding of

I. The risks of congenital malformations and neurodevelopmental disorders for children exposed in utero

- II. The mandatory use of **effective contraception** (preferably an intra-uterine device, or implant, or 2 complementary forms including a barrier method)
 - even if patient has amenorrhea
 - without interruption during the entire valproate treatment duration
 - regardless of sexual activity status
 - refer for contraception services as needed

III. The need to:

- undergo pregnancy testing when required during treatment
- **plan** for pregnancy
- **reassess** bipolar or migraine treatment with you **annually**

Complete the Annual Risk Acknowledgement Form
at initiation and at each annual visit
Provide the Patient Guide



Explain that if she thinks she is pregnant or becomes pregnant, **she should not stop valproate and contact you immediately.**

3

What are the valproate risks if taken during pregnancy?

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

- Congenital malformations,
- Neurodevelopmental disorders.

The risks are dose-related. There is no threshold dose below which no risk exists. Any dose of valproate during pregnancy can be harmful for the unborn child. The nature of the risks for children exposed to valproate during pregnancy is the same irrespective of the indication for which valproate has been prescribed.

Both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes.

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.

Available evidence does not show that folate supplementation prevents birth defects due to valproate exposure⁵.

1. Congenital malformations

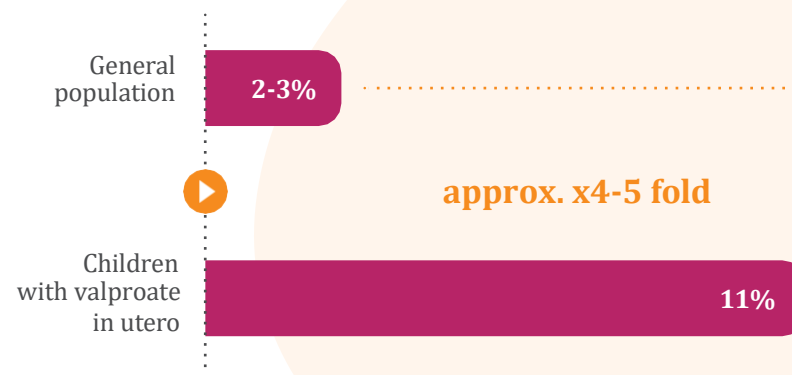
About 11%³ of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations.

This risk is greater than in the general population (about 2-3%).

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.

Risk of congenital malformations



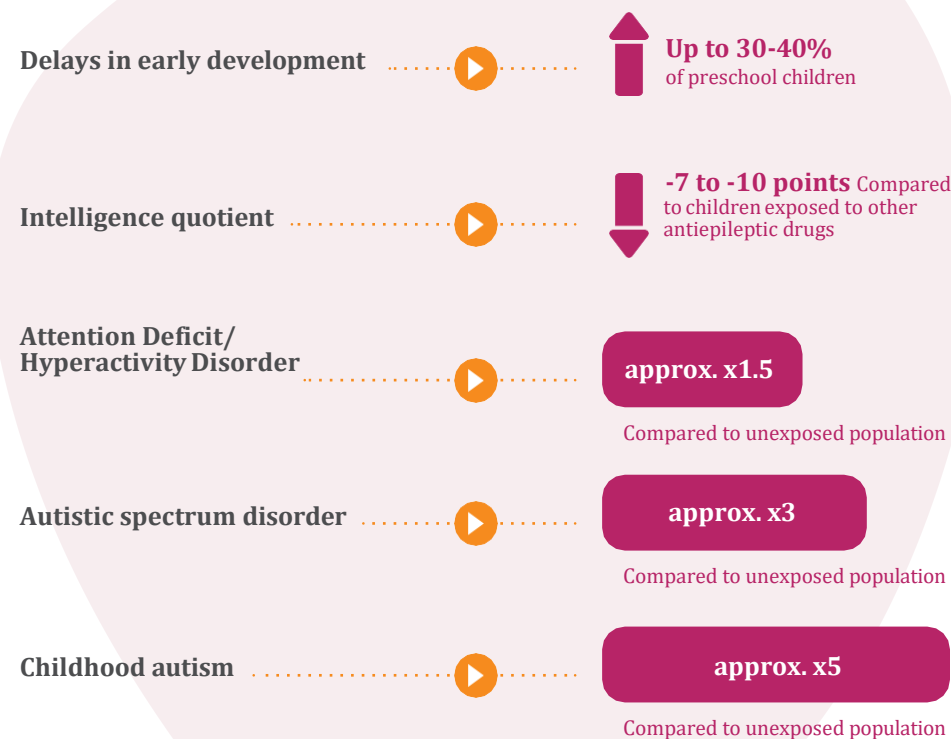
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What are the valproate risks if taken during pregnancy?

2. Neurodevelopmental disorders

- Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children.
- The exact gestational period of risk is uncertain **and the possibility of a risk throughout the entire pregnancy cannot be excluded.**
- Up to 30 or 40% of preschool children exposed in utero may 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 school aged 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 antiepileptics¹⁰.
There are limited data on the long-term outcomes.
- An increased risk in children with a history of valproate exposure in utero compared to the unexposed population:
 - Attention deficit/hyperactivity disorder¹¹: approximately 1.5-fold,
 - Autistic spectrum disorder¹²: approximately 3-fold,
 - Childhood autism¹²: approximately 5-fold.

Risks increased in children exposed to valproate in utero



1

What you must know about the risk to children of fathers treated with valproate in the 3 months prior to 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 men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.

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

Valproate monotherapy group

4.0%-5.6%

Lamotrigine/levetiracetam monotherapy group

2.3%-3.2%

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 the specific NDD subtypes studied (composite endpoint included autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the causal role of valproate is possible but not considered to be 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).

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.

2

What is your role, when managing, treating or taking care of male patients with Epilepsy, Bipolar Disorder or Migraine

SPECIALIST

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 3 months after stopping the treatment
 - To consult a specialist to discuss treatment alternatives when they are planning to

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient.

For male patients planning to conceive a child, suitable treatment alternatives 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, bipolar disorder or migraine should be sought as appropriate.

Provide the Patient Guide

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BD: Bipolar Disorder;

HCP: Health Care Professional;

NDD: Neurodevelopmental Disorders;

WCBP: Women of Childbearing Potential

NOTES

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A handwritten signature in blue ink, appearing to read "G. H. H.", is located on the left side of the page.

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