

VALPROATE
GUIDE

FOR HEALTHCARE PROFESSIONALS

who manage girls,
women of childbearing
potential and men
treated with valproate*

GUIDE ON USE OF VALPROATE

**YOU MUST READ THIS GUIDE CAREFULLY BEFORE ANY
PRESCRIPTION OF VALPROATE**

*This includes brands such as Xolpict Syrup.

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Purpose of this Healthcare Professionals guide

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Purpose of this Healthcare Professionals 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.

See chapter 3 for more information.

Three valproate educational tools have been developed specifically to address this risk.

These tools include:

- This HCP Guide
- 2 Patient Guides
 - One specifically for girls and WCBP
 - One specifically for men of reproductive potential

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

- The prescribing conditions in girls, WCBP and men of reproductive potential,
- The teratogenic and neurodevelopmental risks, associated with the use of valproate during pregnancy, and at time of conception for men,
- The actions necessary to minimize the risks.

HCPs targeted by this guide include:

- Specialists,
- General Practitioners,
- gynecologists/Obstetricians, Midwives, Nurses,
- Pharmacists

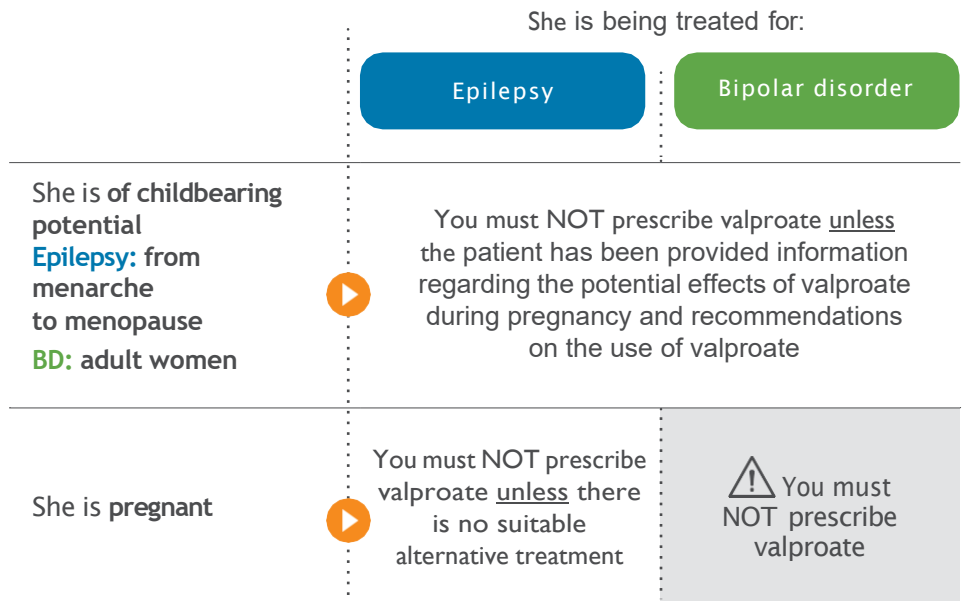
For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal representative/ caregiver and make sure they clearly understand it.

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

1

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

- Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
- It should not be used in female children/adolescents and WCBP unless other treatments are ineffective or not tolerated.



Overview of the Risk Management Strategy (For details read the Product Information)

- 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,

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.

2 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 experiences menarche
- Make efforts to switch her to alternative treatment before she reaches adulthood.

Specialist - Epilepsy

General Practitioner
- Epilepsy

Specialist - Bipolar
Disorder

General Practitioner -
Bipolar Disorder

Obstetrician/Nurse/
Midwife

Pharmacist

SPECIALISTS prescribing valproate to girls and women of childbearing potential for treatment of 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

prescription in women



PLANNING
pregnancy



UNPLANNED
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

The patient should not stop valproate and consult you urgently


▶ 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** epilepsy treatment with you annually

▶ Ensure the patient is aware of the Patient Guide

▶ Specifically for girls

- I. Explain the risks of congenital malformations and neurodevelopmental disorders to the parents/caregivers (and children depending on their age)
- II. 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
- III. Assess the most appropriate time to give advice on contraception
- IV. Reassess the need for valproate therapy at least annually
- V. 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.**

▶ 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

▶ Ensure the patient is aware of 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 experienced in pre-natal=medicine for evaluation and counselling= regarding the exposed pregnancy

GENERAL PRACTITIONERS managing girls and women of childbearing potential who are taking valproate for treatment of **EPILEPSY**

If she is...

NOT PLANNING
a pregnancy

At each visit...

▶ 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
- III. The need to:
 - undergo pregnancy testing when required during treatment
 - **plan for pregnancy**
 - **reassess** epilepsy treatment with her **specialist annually**

▶ Ensure the patient is aware of the Patient Guide

▶ Specifically for girls

- I. Explain the risks of congenital malformations and neurodevelopmental disorders to the parents/caregivers (and children depending on their age)
- II. 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 to consider alternative treatment
- III. Assess the most appropriate time to give advice on contraception

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

If she is...

PLANNING
pregnancy

If she has...

UNPLANNED
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

The patient should not stop valproate and urgently consult her specialist

- ▶
- 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. Refer promptly the patient to her specialist for switching to alternative treatment if suitable
 - III. Tell your patient to continue valproate until her specialist advises her to stop

▶ Ensure the patient is aware of the Patient Guide

Refer your patient and her partner to:

- a gynecologist/obstetrician/midwife
- specialist in experienced in pre-natal medicine for evaluation and= counselling regarding the exposed= pregnancy

SPECIALISTS prescribing valproate to women of childbearing potential for treatment of bipolar disorder

INITIAL valproate prescription

RENEWAL of valproate



Only if:
• other treatments are ineffective or not tolerated
• pregnancy test is negative

NOT PLANNING
a pregnancy

Reassess treatment
at least annually

▶ 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 treatment with you **annually**

▶ Ensure the patient is aware of the Patient Guide

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

prescription in women



PLANNING
pregnancy

UNPLANNED
pregnancy

In bipolar disorder, 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 during pregnancy

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

• Valproate should be discontinued gradually over few weeks to reduce early recurrence ¹

• Discontinue valproate
- Switch to alternative treatment: **a fast cross tapering while installing the alternative treatment is recommended** ²

Refer your patient and her partner to:

- a gynecologist/obstetrician/ midwife
- specialist in experienced in pre-natal medicine for evaluation and= counselling regarding the exposed= pregnancy

▶ Ensure the patient is aware of the Patient Guide

GENERAL PRACTITIONERS managing women of childbearing potential who are taking valproate for treatment of bipolar disorder

If she is...

NOT PLANNING
a pregnancy

At each visit...

▶ 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 amenorrhoea
 - without interruption during the entire valproate treatment duration
 - regardless of sexual activity status
- III. The need to:
 - undergo pregnancy testing when required during treatment
 - **plan** for pregnancy
 - **reassess** bipolar treatment with her **specialist annually**

▶ Ensure the patient is aware of the Patient Guide

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

If she is...

PLANNING
pregnancy

If she has...

UNPLANNED
pregnancy

In polar disorder, valproate is contraindicated during pregnancy

Explain that contraception should only be stopped after complete valproate cessation

The patient should not stop valproate and urgently consult her specialist

- ▶ I. Inform the patient and her partner about the risks
 - to the unborn child exposed to valproate in utero
 - of untreated of bipolar disorder during pregnancy
- II. Refer the patient to her specialist to switch to alternative treatment

▶ Ensure the patient is aware of the Patient Guide

Refer your patient and her partner to:

- a gynecologist/obstetrician/midwife
- specialist in experienced in pre-natal medicine for evaluation and= counselling regarding the exposed= pregnancy

GYNECOLOGISTS, OBSTETRICIANS, MIDWIVES, NURSES managing girls and women of childbearing potential taking valproate

GIRLS and NON-PREGNANT WOMEN
taking valproate

▶ 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
- III. The need to:
 - undergo pregnancy testing when required during treatment
 - **plan** for pregnancy
 - reassess the treatment with her **specialist annually**

▶ Ensure the patient is aware of the Patient Guide

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

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

In bipolar disorder, valproate is contraindicated during pregnancy.

When a woman consults for an EXPOSED PREGNANCY:
REFER HER TO 2 SPECIALISTS

▶ Specialist n° 1

One specialist of the disease for which valproate is prescribed for evaluation and counselling on switch and discontinuation if suitable for her

▶ Specialist n° 2

One specialist in experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy

▶ Ensure the patient is aware of the Patient Guide

PHARMACISTS counselling girls and women of childbearing potential taking valproate

▶ 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 amenorrhoea
 - without interruption during the entire valproate treatment duration
 - regardless of sexual activity status
- III. **The need to:**
 - undergo pregnancy testing when required during treatment
 - **plan for pregnancy**
 - reassess the treatment with her **specialist annually**

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 GUIDE

- Ensure the patient is aware of this guide

- Dispense valproate in the original package, always provide a copy of the Consumer Medicines Information and the outer box if available



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

3

What are the risks if valproate is 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 or malformations 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.

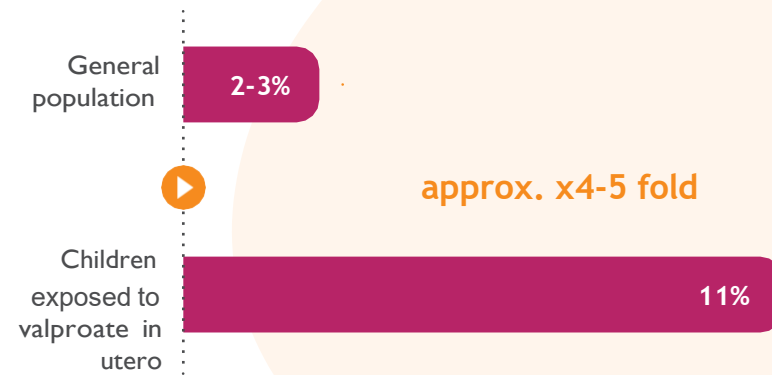
This risk is greater than in the general population (about 2-3%).

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



3

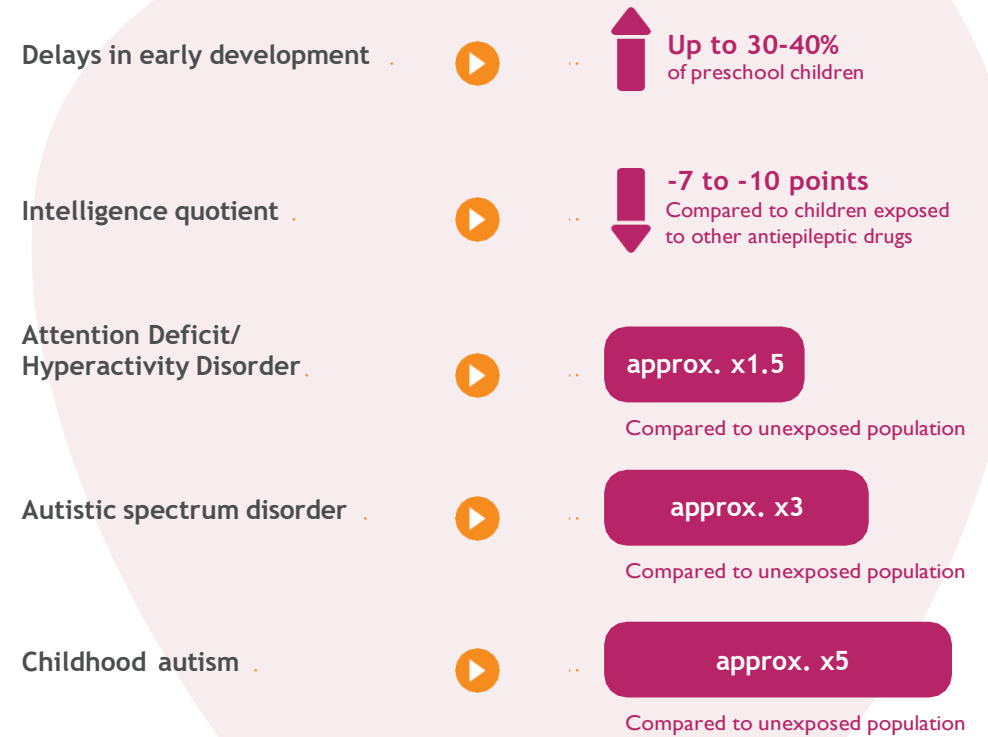
What are the risks if valproate is taken during pregnancy?

2. Neurodevelopmental disorders (NDDs)



- ▶ 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.

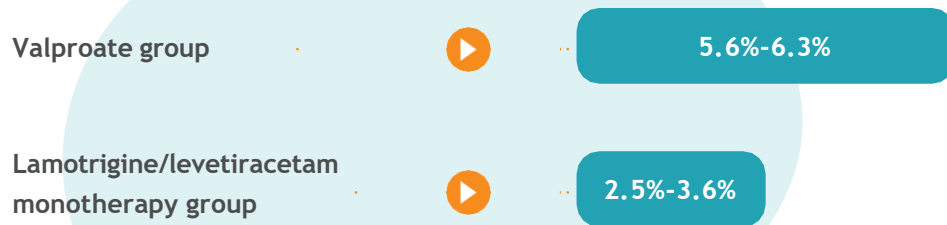
Risks increased in children exposed to valproate in utero



1 What you must know about the potential risk to children of fathers treated with valproate at time of conception

A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of NDDs in children (from 0 to 11 years old) born to men treated with valproate at time of conception compared to those treated with lamotrigine or levetiracetam.

Comparison of risk of NDDs in children born to men treated with valproate at time of conception vs children born to men treated with lamotrigine or levetiracetam



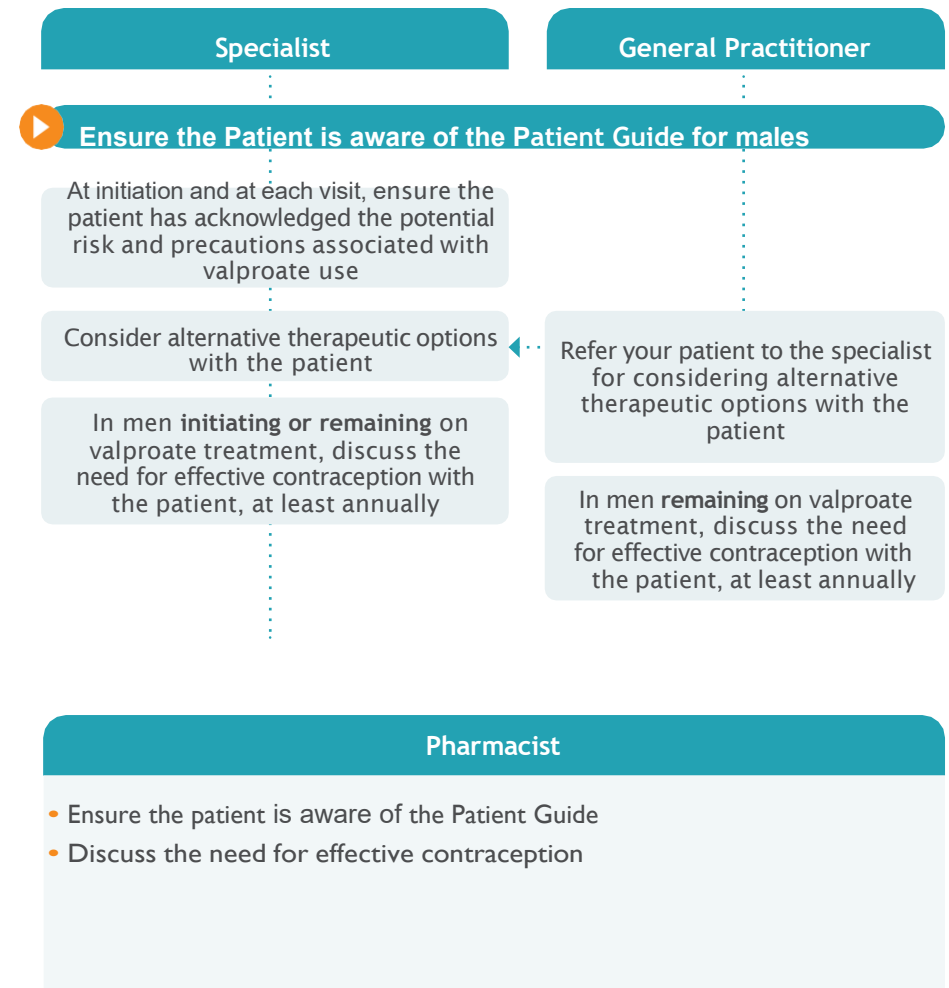
The pooled adjusted hazard ratio for NDDs overall obtained from the meta-analysis of the datasets was 1.47 (95% Confidence Interval: 1.10, 1.96).

Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs.

2 What is your role, when managing men of reproductive potential with Epilepsy or bipolar disorder

As a precautionary measure you should always inform the patient or their caregiver/legal representative of this potential risk.

Additionally, if you are a:



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BD: Bipolar Disorder;
HCP: Health Care Professional;
NDD: Neurodevelopmental Disorders;
WCBP: Women of Childbearing Potential



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