

## Valproate Guide

# **For Healthcare Professionals who manage girls and women of childbearing potential treated with valproate\* (▼ Orfiril, Orfiril long, Orfiril retard)**

## **Guide 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) and women of childbearing potential.

\*Information about valproate use can also be found online at [felleskatalogen.no](http://felleskatalogen.no)

Women who are on seizure prevention drugs during pregnancy are encouraged to register in the EURAP register as part of international monitoring and follow-up.

▼ This medicine is subject to special monitoring to detect new safety information as quickly as possible. Healthcare personnel are encouraged to report any suspected side effects on the electronic reporting form: [www.dmp.no/meldeskjema](http://www.dmp.no/meldeskjema).

# CONTENTS

## Purpose of this Healthcare Professional guide

### GIRLS AND WOMEN OF CHILDBEARING POTENTIAL

1. **What you must know / do about the conditions of valproate prescription in female, girls and adolescent patients? ..... 4-6**
2. **What is your role, when managing, treating or taking care of? ..... 7-19**
  - Girls/ WCBP with epilepsy if you are a
    - Specialist ..... 8-9
    - General practitioner ..... 10-11
  - WCBP with bipolar disorder, if you are a
    - Specialist ..... 12-13
    - General practitioner ..... 14-15
  - Girls/ WCBP with epilepsy, if you are a
    - Gynecologist/Obstetrician, Midwife, Nurse ..... 16-17
    - Pharmacist
3. **What are the valproate risks if taken during pregnancy? ..... 20-23**
  - Congenital malformations
  - Neurodevelopmental disorders

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

## 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.

**See chapter 3 for more information.**

Valproate educational tools have been developed specifically for HCPs and for girls and WCBP treated with valproate.

These tools include:

- this HCP Guide
- an Annual Risk Acknowledgement Form (girls/WCBP)
- a Patient Guide (girls/WCBP)
- a Patient Card (girls/WCPB)

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

- the prescribing conditions in girls and WCBP
- the teratogenic and neurodevelopmental risks, associated with the use of valproate during pregnancy
- 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 Summary of Product Characteristics before prescribing valproate.**

# 1. What you must know / do about the conditions of valproate prescription in female, girls and 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.
- It should be prescribed and dispensed according to the conditions of the valproate Pregnancy Prevention Program.

	She suffers from	
	Epilepsy	Bipolar disorder
She is of childbearing potential <b>Epilepsy:</b> from menarche to menopause <b>BD:</b> 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 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.

## 2. What is your role

Specialist – Epilepsy

General Practitioner – Epilepsy

Specialist – Bipolar disorder

General Practitioner – Bipolar disorder

Gynecologist/Obstetrician/Nurse/Midwife

Pharmacist

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

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

**INITIAL** valproate prescription

**RENEWAL** of valproate

prescription in women

Only if

- Other treatment are ineffective or not tolerated
- Pregnancy test is negative (for WCBP)

**NOT PLANNING** a pregnancy

Reassess treatment at least annually

**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

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**


- 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**

Complete the **Annual Risk Acknowledgement Form** at initiation and at each annual visit  
Provide 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.**

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

**Valproate should preferably be prescribed:**

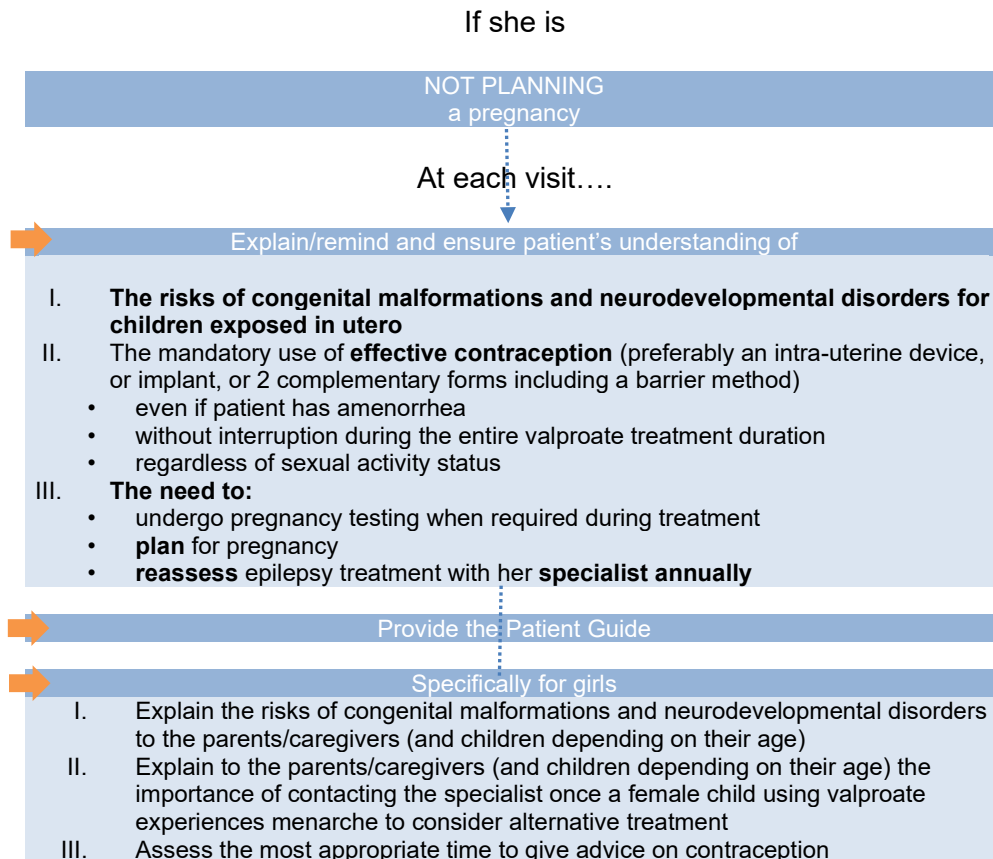
- as monotherapy
- at the lowest effective dose, with daily dose divided into several small doses
- as a prolonged release formulation


**Refer your patient and her partner to:**

- a gynecologist/obstetrician/midwife
- a specialist experienced in assessing birth defects from drugs shall start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

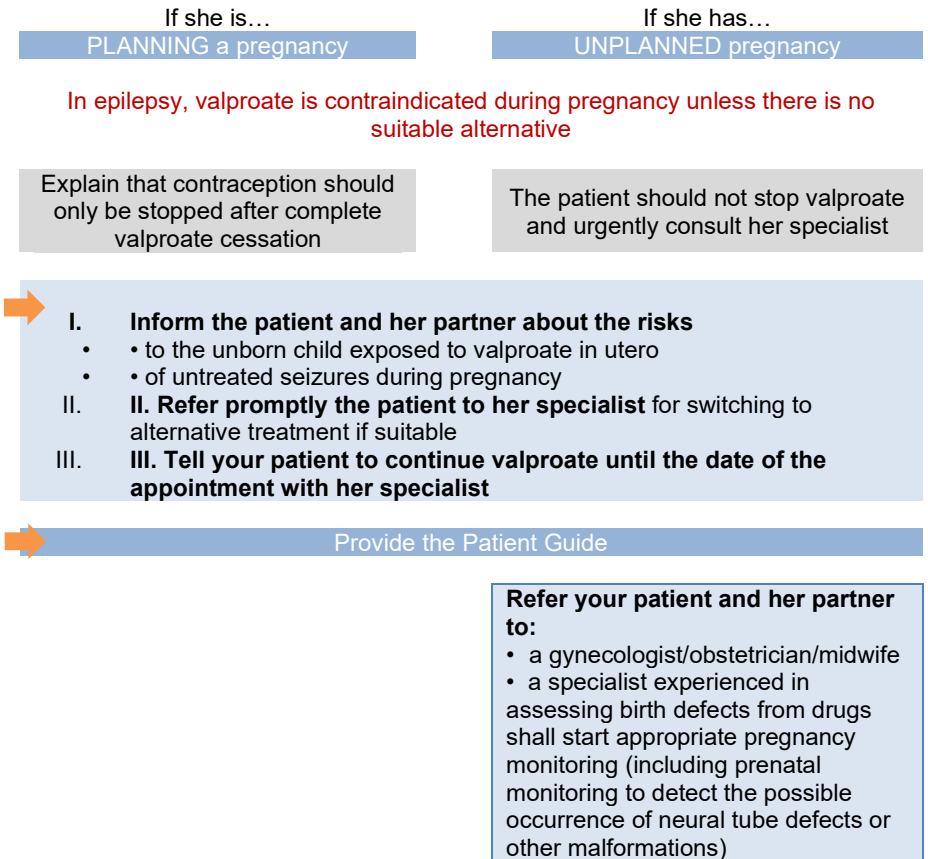


**GENERAL PRACTITIONERS** managing girls and women of childbearing potential who are suffering from **EPILEPSY** and are taking **valproate**



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

FOR ALL PATIENTS: provide and discuss the **patient guide**



**SPECIALISTS** prescribing valproate to girls and women of childbearing potential suffering from **BIPOLAR DISORDER**

**INITIAL** valproate prescription

Only if

- other treatment 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

- IV. **The risks of congenital malformations and neurodevelopmental disorders for children exposed in utero**
- V. 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
- VI. **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**

 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 bipolar disorder, valproate is contraindicated during pregnancy

Switch to alternative treatment prior to conception

**UNPLANNED** pregnancy

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<sup>1</sup>

- Discontinue valproate - Switch to alternative treatment: **a fast cross tapering while installing the alternative treatment is recommended<sup>2</sup>**
- Refer your patient and her partner to:**
- a gynecologist/obstetrician/midwife
  - a specialist experienced in assessing birth defects from drugs shall 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**

What is your role?  
General practitioner –  
Bipolar

**GENERAL PRACTITIONERS** managing women of childbearing potential who are suffering from **BIPOLAR DISORDER** and are taking **valproate**

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**

Provide the Patient Guide

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

FOR ALL PATIENTS: provide and discuss the **patient guide**

If she is...  
PLANNING a pregnancy

If she has...  
UNPLANNED pregnancy

In bipolar 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 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 the date of the appointment with her specialist**

Provide the Patient Guide

**Refer your patient and her partner to:**

- a gynecologist/obstetrician/midwife
- a specialist experienced in assessing birth defects from drugs shall start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

What is your role?  
Gynecologist/  
Obstetrician/Nurse/Midwife

**GYNECOLOGISTS, OBSTETRICIANS, MIDWIFES, 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** epilepsy treatment with her **specialist annually**

Provide the Patient Guide



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

16

FOR ALL PATIENTS: provide and discuss the **patient guide**

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 experienced in assessing birth defects from drugs shall start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

Provide the Patient Guide

17

**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 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**



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

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**FOR ALL PATIENTS:** provide the **patient card**

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

**PATIENT CARD**

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

**PATIENT GUIDE**

- Ensure the patient received it

**ONLINE INFORMATION**

- Remind that online information can also be found by scanning the **QR code on the patient information leaflet**
- Dispense valproate in the original package with an outer warning
- Unpacking should be avoided. If it cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available

### 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.

#### 1. Congenital malformations



About 11%<sup>3</sup> 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:

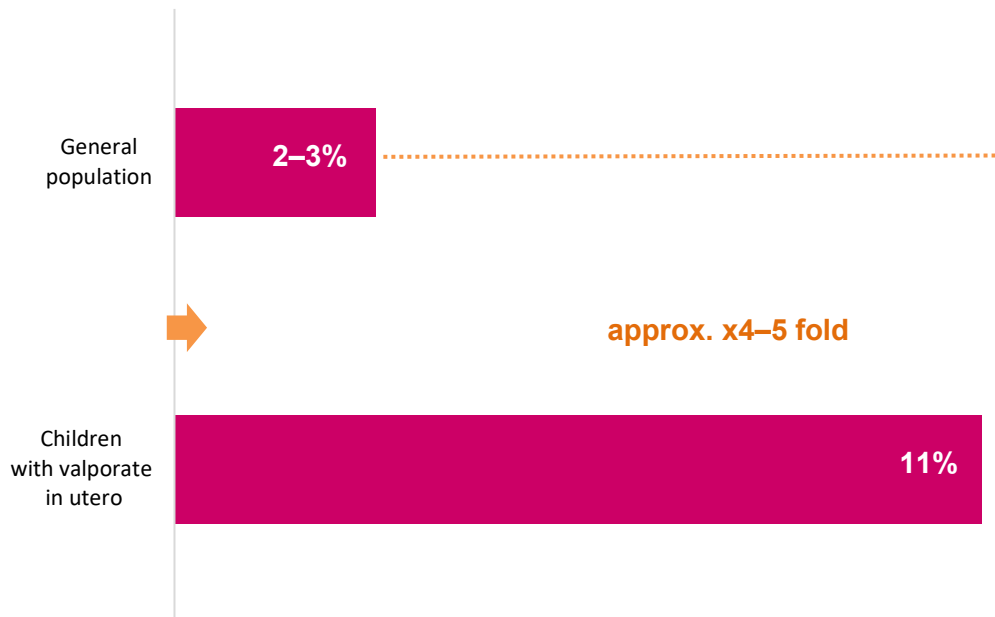
- Neural tube defects
- Facial dysmorphism
- Cleft lip and palate
- Craniostenosis
- Cardiac, renal and urogenital defects
- Limb defects (including bilateral aplasia of the radius)
- Multiple anomalies involving various body systems

In utero exposure to valproate may also result in:

- Unilateral or bilateral hearing impairment or deafness, that may not be reversible<sup>4</sup>,
- 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 exposure<sup>5</sup>.

### Risk of congenital malformations



### 3. What are the valproate risks if taken during pregnancy?

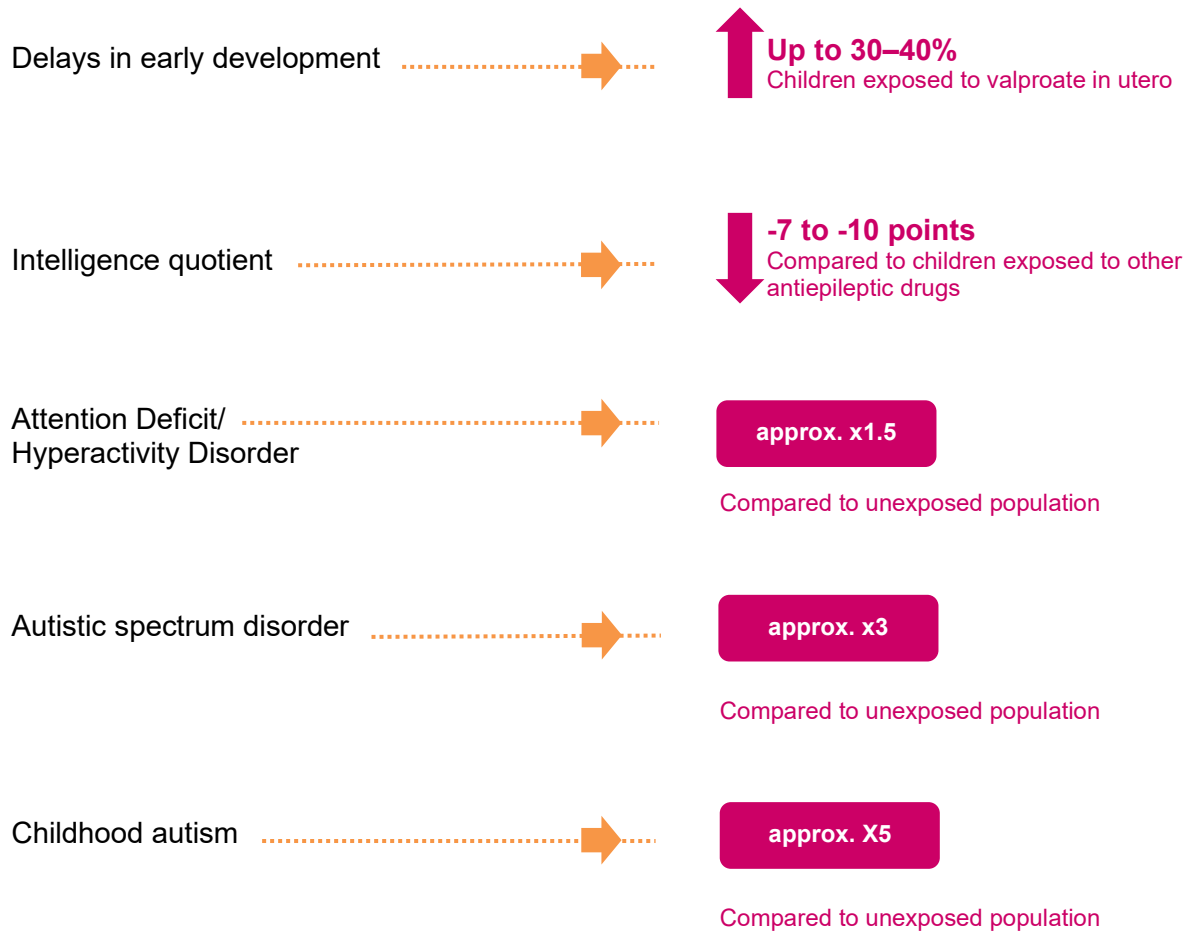
#### 2. Neurodevelopmental disorders



- 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 to 40% of preschool children exposed in utero may experience delays in their early development such as: <sup>6,7,8,9</sup>
  - 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 antiepileptics<sup>10</sup>.  
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 disorder<sup>11</sup>: approximately 1.5-fold,
  - Autistic spectrum disorder<sup>12</sup>: approximately 3-fold,
  - Childhood autism<sup>12</sup>: approximately 5-fold.



## Risks increased in children exposed to valproate in utero



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- <sup>11</sup> 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.
- <sup>12</sup> Christensen J *et al.* Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. *JAMA* 2013; 30



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