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

Information about medicines containing valproate use can also be found in the Product Information (PI), available online at https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili or by scanning the QR code at the end of this document.

*This includes brands such as Epilim, Sodium Valproate Sandoz, Valpro EC and Valproate Winthrop.

CONTENTS

GIRLS AND WOMEN OF CHILDBEARING POTENTIAL

MALE PATIENTS OF REPRODUCTIVE POTENTIAL

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,
- Lower weight at birth for the gestational age.

See chapter 3 for more information.

There is a potential risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception. 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 risks of teratogenicity, neurodevelopmental disorders and lower weight at birth for the gestational age, 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 men of reproductive potential,
- The actions necessary to minimise the risks.

HCPs targeted by this guide include:

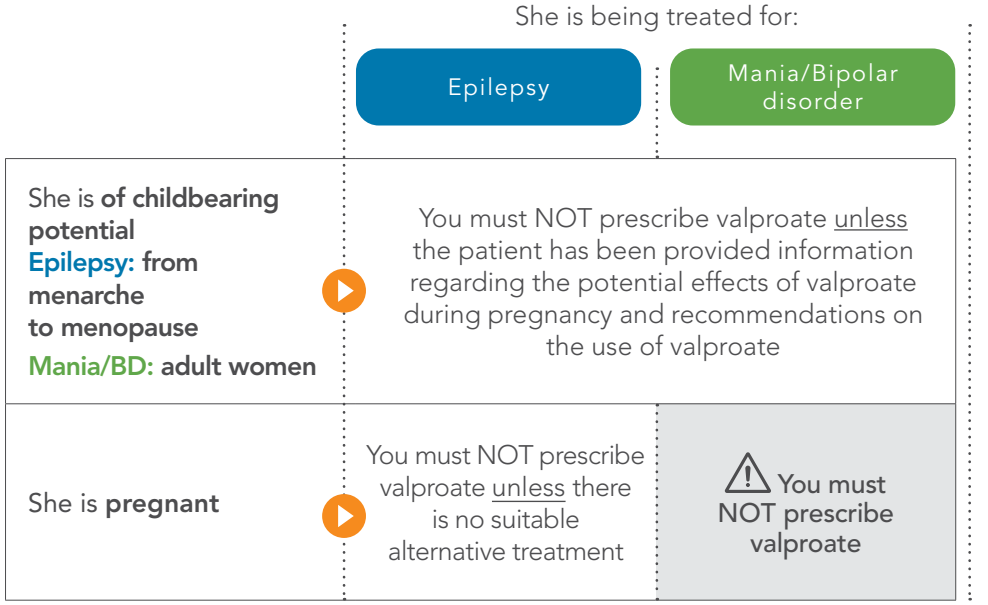
- Specialists,
- General Practitioners,
- Gynaecologists/Obstetricians, Midwives, Nurses,
- Pharmacists.

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 females, girls and adolescents patients?

- Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy, mania (Australia only) or bipolar disorder (New Zealand only).
- 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, neurodevelopmental disorders and lower weight at birth for the gestational age,
- 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,
- Direct patients to the Patient Guide, available online at https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili or by scanning the QR code on the box

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, neurodevelopmental disorders and lower weight at birth for the gestational age
- 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 - Mania/Bipolar Disorder

General Practitioner - Mania/Bipolar Disorder

Gynaecologist/Obstetrician/ Nurse/Midwife

Pharmacist

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

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

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

I. The risks of congenital malformations, neurodevelopmental disorders and lower weight at birth for the gestational age 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
- referral 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, neurodevelopmental disorders and lower weight at birth for the gestational age 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 girls 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.**

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

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 gynaecologist/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, neurodevelopmental disorders and lower weight at birth for the gestational age 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, neurodevelopmental disorders and lower weight at birth for the gestational age 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.**

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

If she is... | If she has...

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 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 gynaecologist/obstetrician/ midwife
- specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy

SPECIALISTS prescribing valproate to women of childbearing potential for treatment of MANIA (Australia only) or BIPOLAR DISORDER (New Zealand only)

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

INITIAL valproate prescription

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

RENEWAL of valproate

NOT PLANNING a pregnancy

Reassess treatment **at least annually**

Prescription in women

PLANNING pregnancy

UNPLANNED pregnancy

In mania or 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 initiating the alternative treatment is recommended** [2]

Refer your patient and her partner to:
- a gynaecologist/obstetrician/ midwife
- specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy

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 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
- referral for contraception services as needed

III. The need to:
- undergo pregnancy testing when required during treatment
- **plan** for pregnancy
- **reassess** mania or bipolar disorder 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.**

Ensure the patient is aware of the Patient Guide

GENERAL PRACTITIONERS managing women of childbearing potential who are taking valproate for treatment of MANIA (Australia only) or BIPOLAR DISORDER (New Zealand only)

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

If she is...

NOT PLANNING a pregnancy

At each visit...

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 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** mania or bipolar disorder 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 mania or 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 mania or 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 gynaecologist/obstetrician midwife
- specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy

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

GYNAECOLOGISTS, 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, neurodevelopmental disorders and lower weight at birth for the gestational age 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.**

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

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

In mania or 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 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**

FOR ALL PATIENTS: Ensure the patient is aware of and discuss the patient guide which is available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili).

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

In mania or bipolar disorder, valproate is contraindicated during pregnancy.

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 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**

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

About educational materials

Patient Guide
- Ensure the patient is aware of this guide and that it can be found by scanning the QR code on the box
- 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 Consumer Medicines Information and the outer box if available

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,
- Lower weight at birth for the gestational age.

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

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

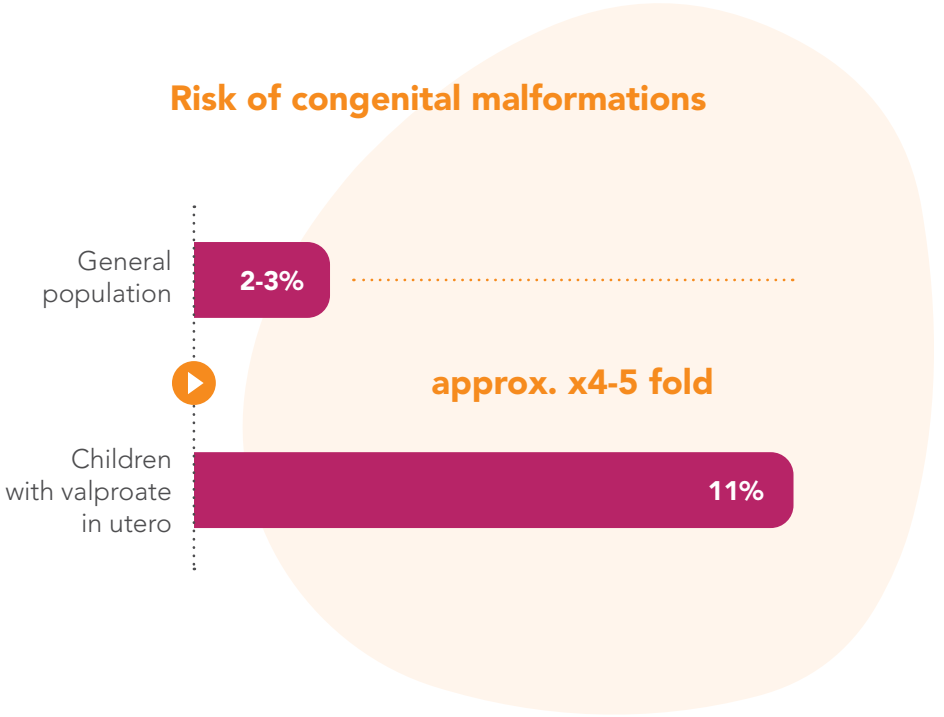
Available data show an increased incidence of minor or major malformations. The most common types of malformations included:

- 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[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 exposure[5].



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 to 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 antiepileptics[10].

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[11]: approximately 1.5-fold,
- Autistic spectrum disorder[12]: approximately 3-fold,
- Childhood autism[12]: approximately 5-fold.

Risks increased in children exposed to valproate in utero

Delays in early development	**Up to 30-40%** of preschool children
Intelligence quotient	**-7 to -10 points** Compared to children exposed to other antiepileptic drugs
Attention Deficit/ Hyperactivity Disorder	**approx. x1.5** Compared to unexposed population
Autistic spectrum disorder	**approx. x3** Compared to unexposed population
Childhood autism	**approx. x5** Compared to unexposed population

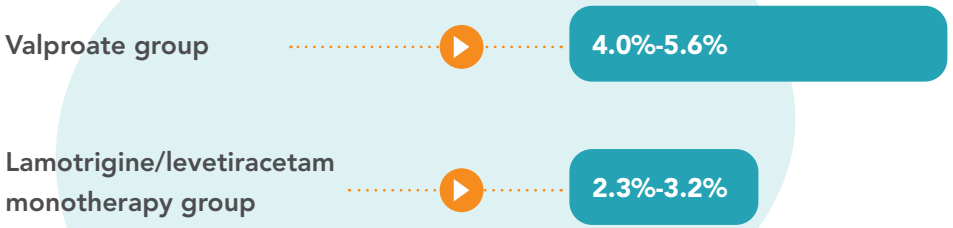
3. Lower weight at birth for the gestational age

▶ 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.

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

Comparison of 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



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).

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.

The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

2 What is your role when managing men of reproductive potential with Epilepsy, Mania (Australia only) or Bipolar Disorder (New Zealand only)

SPECIALIST and GENERAL PRACTITIONER

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. There are no data on this potential risk to children fathered more than 3 months after stopping valproate treatment (i.e., allowing a new spermatogenesis without valproate exposure)

III. By way of precaution, discuss with the patient, at least annually, **the need**:

- for **effective contraception,** including for the female partner, while using valproate and for 3 months after stopping the treatment
- **not to donate sperm** during treatment and for 3 months after stopping the treatment
- to consult his doctor **to discuss alternative treatment options,** as soon as he is planning to father a child and before discontinuation of contraception
- for him and his female partner to contact their doctor for counselling **in case of pregnancy** if he used valproate within 3 months prior to conception

PHARMACIST

- Ensure the patient is aware of the Guide for men of reproductive potential, available electronically through the QR code located on the box (https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili)
- Discuss the need for effective contraception

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BD: Bipolar Disorder;

HCP: Health Care Professional;

NDD: Neurodevelopmental Disorders;

WCBP: Women of Childbearing Potential

Please review full Product Information before prescribing.
Full Product Information is available from sanofi-aventis australia pty ltd by scanning the adjacent QR code, at https://qr.medsinfo.com.au/tx/sw.cfm?h=swcepili or by contacting 1800 818 806.

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