

**VALPROATE
GUIDE**

FOR HEALTHCARE PROFESSIONALS

**who manage girls and women
of childbearing potential
treated with Valproate*
(Depalept Chrono)**

VALPROATE

Please also refer to the Summary
of Product Characteristics

Includes information on use
of Valproate in
accordance with the
pregnancy prevention

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

* Valproate is a generic term including Valproic acid, Valproate sodium, Valproate semisodium, Valproate magnesium, and Valpromide.

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Purpose of this Healthcare Professional guide

GIRLS AND WOMEN OF CHILDBEARING POTENTIAL

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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.

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
- A Physician Checklist (girls/WCBP)
- A Patient Guide (girls/WCBP)
- A Patient Card (girls/WCBP)

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:

- Neurologists,
- Psychiatrists,
- General Practitioners,
- Gynecologists,
- Pharmacists

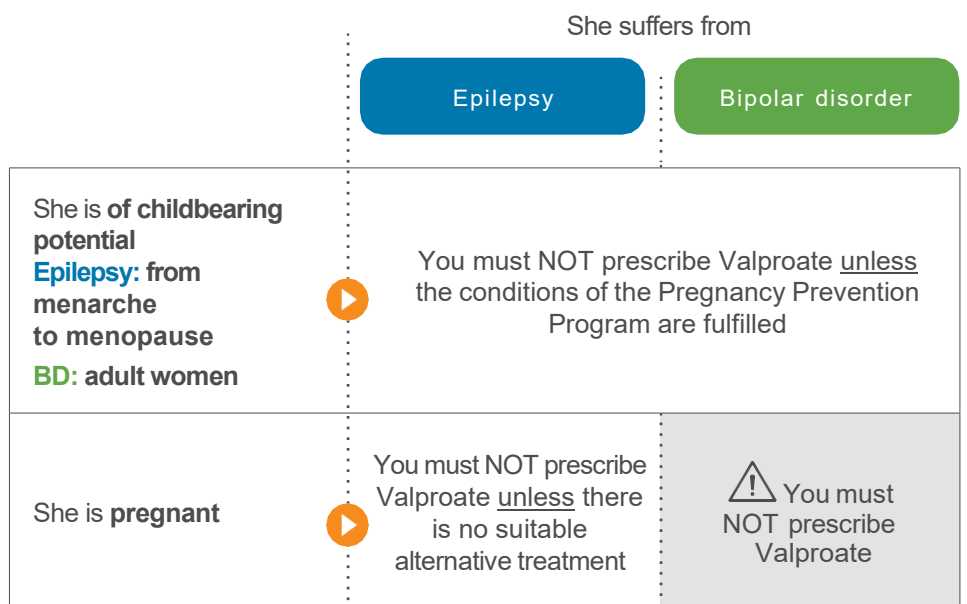
For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal representative/ caregiver and make sure they clearly understand it.

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 adolescents patients?

- Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder (neurologist or psychiatrist).
- It should not be used in female girls/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.



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 Physician Checklist with the patient at initiation and or 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 neurologist 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.

Neurologist - Epilepsy

General Practitioner
- Epilepsy

Psychiatrist - Bipolar Disorder

General Practitioner
- Bipolar Disorder

Gynecologist

Pharmacies

NEUROLOGISTS prescribing Valproate to girls and women of childbearing potential suffering from EPILEPSY

INITIAL Valproate

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 to a gynecologist 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 Physician Checklist 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 girl depending on their age)
- Explain to the parents/caregivers (and girl depending on their age) the importance of contacting the specialist once a girl 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 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.

FOR ALL PATIENTS: complete the **Physician Checklist** at initiation and annually;
provide and discuss the **patient guide**

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

- Inform the patient and her partner about the risks**
 - to the unborn child exposed to Valproate in utero
 - of untreated seizures during pregnancy
- 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 or months - commonly 2-3 months
- If a seizure occurs during Valproate withdrawal, maintain the minimum required dose**

Complete the Physician Checklist 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 at least two individual doses
- as a prolonged release formulation

Refer your patient and her partner to:

- a gynecologist for pregnancy monitor
- a specialist experienced in teratology or prenatal medicine for 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**

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 **neurologist annually**

▶ Provide the Patient Guide

▶ Specifically for girls

- I. Explain the risks of congenital malformations and neurodevelopmental disorders to the parents/caregivers (and girl depending on her age)
- II. Explain to the parents/caregivers (and the girl depending on her age) the importance of contacting the neurologist once a girl using Valproate experiences menarche to consider alternative treatment
- III. Assess the most appropriate time to give advice on contraception

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

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 neurologist

- ▶ 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 neurologist for switching to alternative treatment if suitable
- III. Tell your patient to continue Valproate until the date of the appointment with her neurologist

▶ Provide the Patient Guide

Refer your patient and her partner to:

- a gynecologist for pregnancy monitor
- specialist in teratology or prenatal medicine for prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations

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

PSYCHIATRISTS prescribing Valproate to girls and women of childbearing potential suffering from **BIPOLAR DISORDER**

INITIAL Valproate



- 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

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 of symptoms¹

- 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 for pregnancy monitor
- a specialist experienced in teratology or prenatal medicine for prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations



**Complete the Physician Checklist at initiation and at each annual visit
Provide the Patient Guide**



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 to a gynecologist for contraception services as needed
- The need to:**
 - undergo pregnancy testing when required during treatment
 - **plan** for pregnancy
 - **reassess** bipolar treatment with you **annually**



**Complete the Physician Checklist 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.**

GENERAL PRACTITIONERS managing girls and 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** bipolar treatment with her **psychiatrist annually**



Provide the Patient Guide

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

If she is...

PLANNING
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 psychiatrist



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



Provide the Patient Guide

Refer your patient and her partner to:

- a gynecologist for pregnancy monitor
- specialist in teratology or prenatal medicine for prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations



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

GYNECOLOGISTS, 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 respective **specialist (neurologist or psychiatrist) 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 (neurologist or psychiatrist) immediately.**

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 (neurologist or psychiatrist) for evaluation and counselling on switch and discontinuation if suitable for her

▶ Specialist n°2

One specialist in teratology or prenatal medicine to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations) for evaluation and counselling

▶ Provide 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 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 respective **specialist (neurologist or psychiatrist) annually**

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.



About educational materials

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



Explain that if she thinks she is pregnant or becomes pregnant, **she should not stop Valproate and contact her specialist (neurologist or psychiatrist) 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.

Children exposed to valproate in utero also have a higher risk of being born small for gestational age.

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

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 3% at birth).

Available data show an increased incidence of minor or major malformations.

The most common types of malformations included:

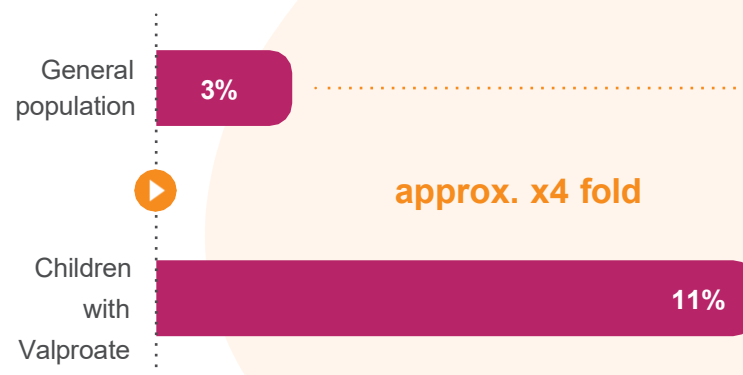
- Neural tube defects
- Facial dysmorphism
- Cleft lip and palate
- Craniostenosis
- Cardiac, renal and urogenital defects
- Limb defects (including bilateral aplasia of the radius)
- Multiple anomalies involving various body systems.

In utero exposure to Valproate may also result in:

- Unilateral or bilateral hearing impairment or deafness, that may not be reversible⁴,
- 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.

Risk of congenital malformations



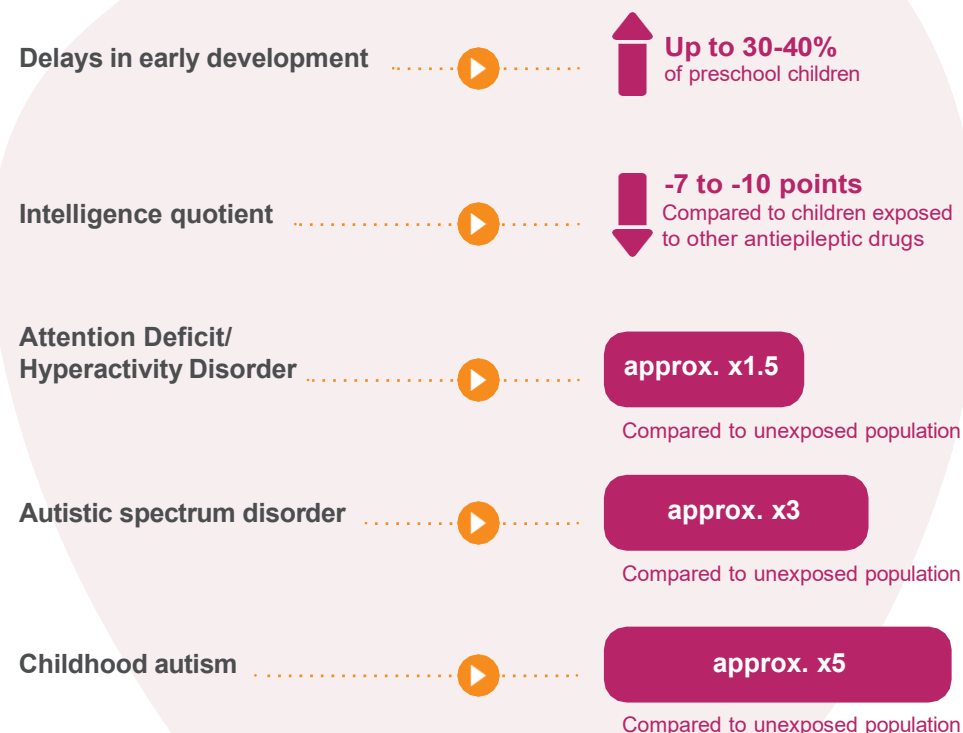
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What are the Valproate risks if taken during pregnancy?

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 disorder (ADHD)¹¹: approximately 1.5-fold increase,
 - Autistic spectrum disorder¹²: approximately 3-fold increase,
 - Childhood autism¹²: approximately 5-fold increase.

Risks increased in children exposed to Valproate in utero



3. Small for gestational age

- Some epidemiological studies¹³⁻¹⁴ have suggested a higher risk of being born small for gestational age (SGA 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. SGA was observed in approximately 11-15% of children exposed to valproate in utero, 8-9% of lamotrigine-exposed children, and 5-10% of unexposed children.

Available data in human do not allow to conclude on a potential dose-related effect.

REFERENCES

1. Malhi GS, Bassett D, Boyce P, *et al.* Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand J. Psychiatry 2015, Vol. 49(12):1-185.
2. Minutes and answers from the SAG Psychiatry meeting on Valproate-EMA/679681/2017.
3. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounscome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.
4. Foch C, Araujo M, Weckel A, Damase-Michel C, Montastruc JL, Benevent J, *et al.* In utero drug exposure and hearing impairment in 2-year-old children A case-control study using the EFEMERIS database. Int J Pediatr Otorhinolaryngol. 2018 Oct;113:192-7.
5. Jentink J, Bakker MK, Nijenhuis CM, Wilffert B, de Jong-van den Berg LT. Does folic acid use decrease the risk for spina bifida after in utero exposure to valproic acid? Pharmacoepidemiol Drug Saf. 2010 Aug;19(8):803-7.
6. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L *et al.* Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October; 51(10):2058-65.
7. Cummings *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;96:643-647.
8. Meador K *et al.* Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009; 360 (16):1597-1605.
9. Thomas S.V *et al.* Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008 (13):229-236.
10. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013 Mar; 12(3):244-52.
11. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalgaard 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.
12. Christensen J *et al.* Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. *JAMA* 2013; 309(16):1696-1703.
13. Kilic D, Pedersen H, Kjaersgaard MI, Parner ET, Vestergaard M, Sørensen MJ *et al.* Birth outcomes after prenatal exposure to antiepileptic drugs--a population-based study. *Epilepsia*. 2014 Nov;55(11):1714-21.
14. Hernández-Díaz S, McElrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB; North American Antiepileptic Drug Pregnancy Registry. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. *Ann Neurol*. 2017 Sep;82(3):457-65.

BD: Bipolar Disorder;

HCP: Health Care Professional;

NDD: Neurodevelopmental Disorders;

WCBP: Women of Childbearing Potential

Healthcare professionals are asked to report any suspected adverse reactions to the ministry of health by means of the online form for reporting adverse reactions located at:
<https://reportsideffect.health.gov.il/drugs/home>
Additionally, may be reported to Sanofi Israel Pharmacovigilance:
PV.Israel@sanofi.com

The Ministry of Health has approved the format and the content of Health Care Professional guide in July 2026.

NOTES

The Sanofi logo is centered in the lower half of the image. It consists of the word "sanofi" in a lowercase, sans-serif font. The first dot of the "s" and the second dot of the "i" are colored purple, while the remaining letters are black. The logo is positioned below a thick, wavy orange line that separates the white foreground from the dark green background above.

sanofi