VALPROATE GUIDE

NEW INFORMATION MAY 2024

FOR HEALTHCARE PROFESSIONALS

who manage girls and women of childbearing potential and male patients treated with valproate (Epilim)

prevent
valproate pregnancy prevention programme

Includes information on use of valproate in girls and women of childbearing potential in accordance with the pregnancy prevention program.

Also includes information on precautionary measures in **male** patients.

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

Electronic copies of this Guide and other materials related to the valproate pregnancy prevention programme can also be found online at www.hpra.ie.
Enter «Epilim» or «valproate» in the search box and then click on «EdM» next to any of the medicines that appear.

THIS GUIDE HAS BEEN APPROVED BY THE HEALTH PRODUCTS REGULATORY AUTHORITY

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

Purpose of this Healthcare Professional Guide

Girls and Women of Childbearing Potential

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.

Male Patients

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

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

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

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

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

HCPs targeted by this guide include:

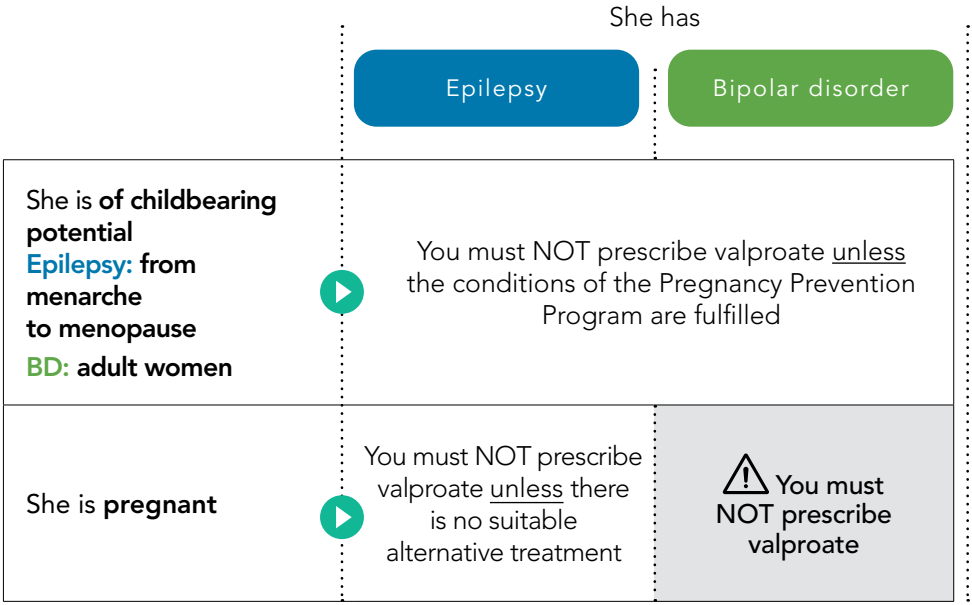
- Specialists,
- General Practitioners,
- Gynaecologists/Obstetricians, Midwives,
- Pharmacists

For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal guardian/ 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 Conditions of valproate prescription in girls and women of childbearing potential

- Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. This is defined as a consultant psychiatrist or a consultant neurologist who regularly manages a bipolar disorder or complex epilepsy.
- It should not be used in girls 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

(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 her doctor 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.

Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.

What you must do if you are managing a girl 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.

2 What is your role?

- Specialist – Epilepsy
- General Practitioner – Epilepsy
- Specialist – Bipolar
- General Practitioner – Bipolar
- Gynaecologist/Obstetrician/ Midwife
- Pharmacist

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

INITIAL valproate prescription

Only if:
- other treatments are ineffective or not tolerated
- pregnancy test is negative **& conditions of PPP are fulfilled** (for WCBP)

RENEWAL of valproate prescription in women

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 requirement to use **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**

Complete and sign 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 you once a girl 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 girls to alternative treatment before they reach adulthood

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

RENEWAL of valproate 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:
- switching to an alternative medication should be undertaken in accordance with clinical practice and available guidelines, as appropriate

Complete and sign the Annual Risk Acknowledgement Form. Provide the Patient Guide.

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

Valproate should preferably be prescribed:
- as monotherapy
- at the lowest effective dose, with daily dose divided into several small doses
- as a prolonged release formulation

Refer your patient and her partner to:
- an obstetrician to 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 with **EPILEPSY** who 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 requirement to use **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

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 you for specialist referral once a girl using valproate experiences menarche to consider alternative treatment

III. Assess the most appropriate time to give advice on contraception

All female patients: 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 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 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. Promptly refer the patient to her specialist
for switching to alternative treatment if suitable
Ask for her to be seen urgently (within days) in case of unplanned pregnancy

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:
- an obstetrician to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

SPECIALISTS prescribing valproate to women of childbearing potential with **BIPOLAR DISORDER**

INITIAL valproate prescription

Only if:
- other treatments are ineffective or not tolerated
- pregnancy test is negative **& conditions of the PPP are fulfilled** (for WCBP)

RENEWAL of valproate prescription in women

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 requirement to use **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**

Complete and sign 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.**

RENEWAL of valproate 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 in accordance with clinical practice and available guidelines, as appropriate

- Discontinue valproate
  - Switch to alternative treatment

Refer your patient and her partner to:

- an obstetrician to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

Complete and sign the Annual Risk Acknowledgement Form. Provide the Patient Guide.

GENERAL PRACTITIONERS managing women of childbearing potential with BIPOLAR DISORDER who 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 requirement to use **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 **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 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 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. Promptly refer the patient to her specialist to switch
to alternative treatment
Ask for her to been seen urgently (within days) in case of an unplanned pregnancy

Provide the Patient Guide

Refer your patient and her partner to:
- an obstetrician to start appropriate pregnancy monitoring (including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations)

GYNAECOLOGISTS, OBSTETRICIANS, MIDWIVES
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 requirement to use **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 **the specialist for her epilepsy or bipolar disorder annually**

Ensure she has the Patient Guide and provide a copy if necessary

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

Ensure she has the Patient Guide and provide a copy if necessary

PHARMACISTS counselling girls and women of childbearing potential taking **valproate**

Remind and ensure patient's understanding of

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

II. The requirement to use **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
- If a woman of childbearing potential reports that she is not using effective contraception, refer her to her GP

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.**

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 with them

PATIENT GUIDE
- Ensure the patient received it

ONLINE INFORMATION
- Remind the patient that online information can also be found by scanning the **QR code** which is included in the patient leaflet and on the outer carton

- **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 patient leaflet and patient card and add a sticker with the warning to the outer packaging**

3 What are the risks of valproate if taken by female patients 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. However, a threshold dose below which no risk exists cannot be established. 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%[1] 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%).

The risk of major congenital malformations in children exposed to polytherapy including valproate during pregnancy is higher than that of anti-epileptic drug polytherapy not including valproate.

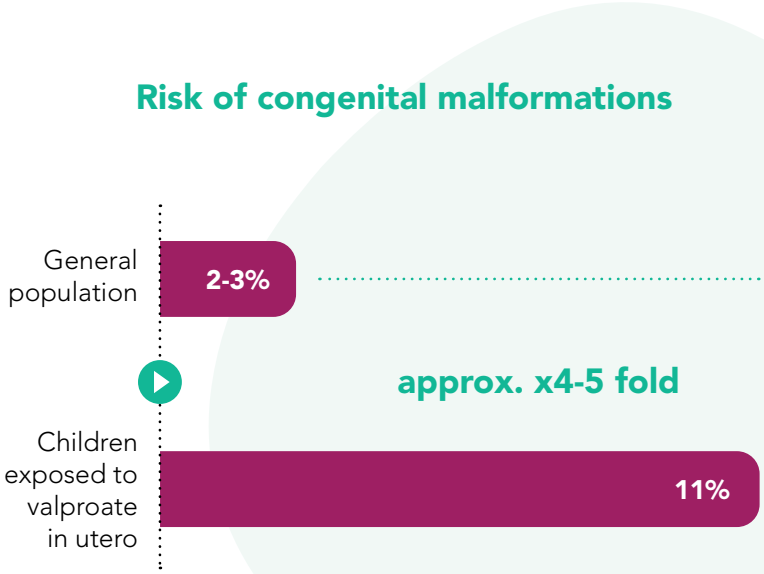
Available data show an increased incidence of minor or major malformations. The most common types of malformations included:

- 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 [2],
- 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[3].



3 What are the risks of valproate if taken by female patients during pregnancy?

2. Neurodevelopmental disorders

▶ Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children.

▶ When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders were also significantly increased as compared with those in children from the general population or born to untreated epileptic mothers.

▶ 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: [4-7]

- 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[8].

There are limited data on the long-term outcomes.

▶ There is also an increased risk in children with a history of valproate exposure in utero compared to the unexposed population for the following neurodevelopmental disorders:

- Attention deficit/hyperactivity disorder[9]: approximately 1.5-fold,
- Autistic spectrum disorder[10]: approximately 3-fold,
- Childhood autism[10]: 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

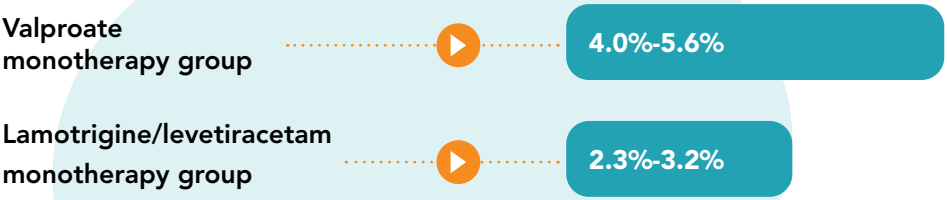
Compared to unexposed population

Male Patients

1 What is the potential risk to children of fathers treated with valproate in the 3 months prior to conception?

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.

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



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).

STUDY LIMITATIONS

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

The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

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

It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.

SPECIALIST and GENERAL PRACTITIONER

Explain/remind and ensure patient's knowledge of

- **The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception.**
- Discuss with the patient regularly **the need**:
  - To consider **effective contraception**, including for a female partner, while using valproate and for at least 3 months after stopping the treatment.
- Male patients **should not donate sperm** during treatment and for at least 3 months after treatment discontinuation.

- Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient.
- For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.
- It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Provide the Patient Guide

PHARMACIST

- Ensure the patient received the Patient Guide and Patient Card
- Remind the patient that online information can also be found by scanning the **QR code** which is included in the patient leaflet and on the outer carton

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NOTES

NOTES

NOTES

BD: Bipolar Disorder;

HCP: Health Care Professional;

NDD: Neurodevelopmental Disorders;

WCBP: Women of Childbearing Potential

For further copies of this Guide please contact Sanofi medical information department on

01 403 5600 or email **IEmedinfo@sanofi.com**

Adverse event reporting

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events via HPRA Pharmacovigilance. Website:* **www.hpra.ie**

Adverse events should also be reported to the Sanofi drug safety department: Tel: **01 403 5600***; Email:* **IEPharmacovigilance@sanofi.com**

HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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