GUIDE ON VALPROATE

GUIDE FOR HEALTHCARE PROFESSIONALS

treating girls and women of childbearing potential and male patients treated with valproate*

Includes information on the use of valproate in accordance with a pregnancy prevention programme

READ THIS GUIDE CAREFULLY BEFORE PRESCRIBING VALPROATE TO GIRLS (REGARDLESS OF AGE), WOMEN OF CHILDBEARING POTENTIAL AND MALE PATIENTS

Information on the use of valproate can also be found online at www.walproiniany.pl

▼ Valproate - this medicinal product will be additionally monitored.
This will enable new information on the safety of the drug to be identified quickly.
The user of the medicine can also help by reporting any adverse reactions that occurred after using the medicine (see section 4.8 of the Summary of Product Characteristics).

* Valproate is a generic name that includes valproic acid, sodium valproate, semi-sodium valproate, magnesium valproate and valpromide.

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BPAD: bipolar affective disorder

Purpose of this Guide for Healthcare Professionals

The use of valproate during pregnancy is harmful to the foetus. In children exposed to valproate in foetal life, there is an increased risk of:

- birth defects
- neurodevelopmental disorders

There is a potential risk of neurodevelopmental disorders in children of fathers treated with valproate within the 3 months before the conception.

Educational tools on valproate have been developed specifically for healthcare professionals and both female and male patients. These include:

- this Guide for Healthcare Professionals
- annual risk acknowledgement form (for females only)
- 2 different Patient Guides (for females and males)
- Patient Card

This guide aims to provide all healthcare professionals involved in patient care with information on:

- conditions for prescribing valproate to girls, women of childbearing potential and male patients;
- the risk of teratogenic effects and the occurrence of neurodevelopmental disorders associated with the use of valproate during pregnancy;
- the potential risk of neurodevelopmental disorders associated with valproate use within the 3 months prior to conception in male patients;
- measures necessary to minimise these risks.

This guide is aimed at the following healthcare professionals:

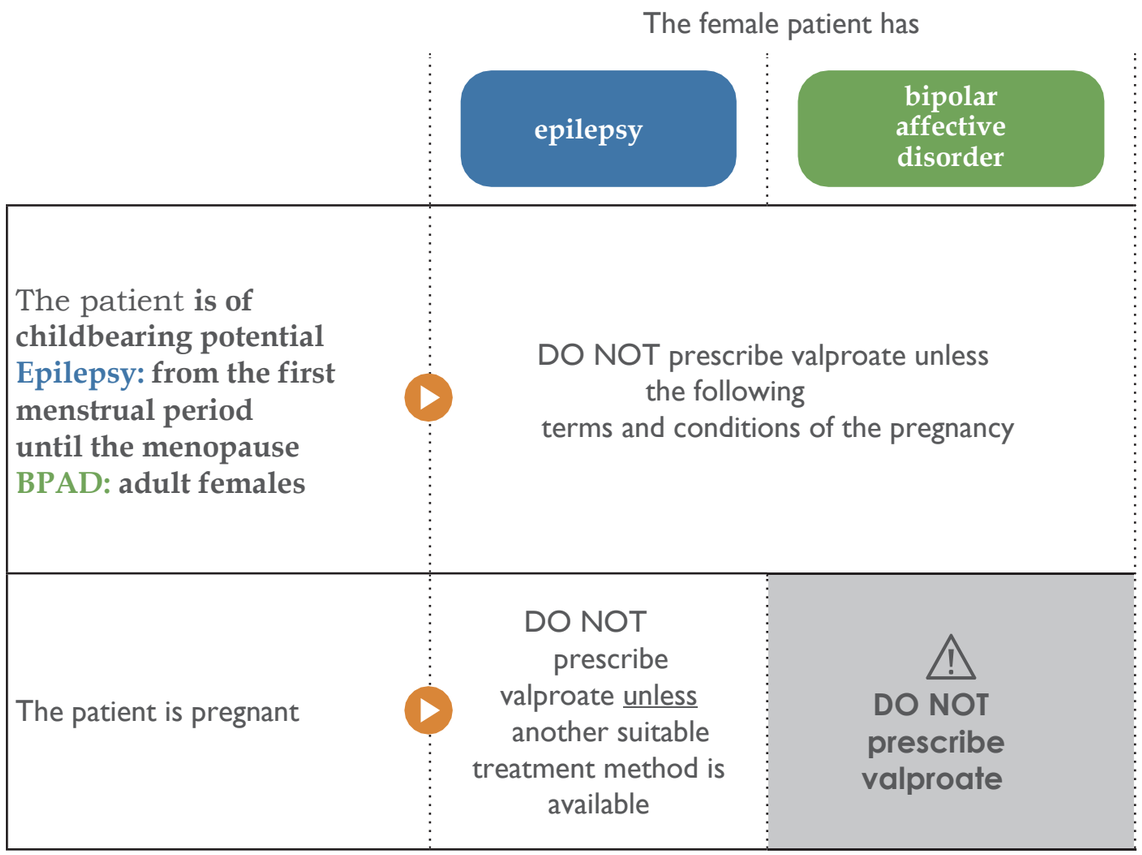
- specialist doctors
- family doctors
- gynaecologists/obstetricians, midwives, nurses
- pharmacists

In the case of patients who are minors or incapable of making an informed decision, provide this information to their parents/legal representative/guardian and ensure that the information is fully understood.

Before prescribing valproate to patients, read the most recent version of the Summary of Product Characteristics.

1 What do you need to know/do in the context of conditions for prescribing valproate to women, girls and adolescents?

- Treatment with valproate must be implemented and supervised by a specialist with experience in the treatment of epilepsy or bipolar affective disorder.
- It should not be used in children/female adolescents or women of childbearing potential, unless other methods of treatment are ineffective or not tolerated.
- The drug should be prescribed and dispensed according to the terms of the pregnancy prevention programme while taking valproate.



Review of the terms and conditions of the pregnancy prevention programme (see the Summary of Product Characteristics for details)

- Assessment of whether the patients could become pregnant
- Explaining the risk of birth defects and neurodevelopmental disorders
- Performing pregnancy tests before and during treatment, as needed
- Advice on the need to use effective contraception throughout the entire treatment period
- Explaining the need for pregnancy planning
- Explaining the need to consult a doctor urgently if you become pregnant
- A regular (carried out at least once a year) assessment of treatment by a specialist doctor
- Handing over the Patient Guide
- Completing together with the patient the annual risk acknowledgement form at the start of treatment and during the annual assessment.

These conditions also apply to women who are not currently sexually active, unless the prescribing physician considers that there are significant reasons indicating that there is no risk of pregnancy.

What to do when taking care of girls/adolescents treated with valproate

- Explain the risks of birth defects and neurodevelopmental disorders to the patient or her parents/guardians (depending on age).
- Explain to the patient or her parents/guardians the importance of contacting a specialist after the onset of her first menstrual period.
- Reassess the appropriateness of valproate treatment at least once a year and consider other methods of treatment immediately after the onset of the first menstrual period.
- Make every effort to change the patient's treatment to another method before she reaches adulthood.

2 What is the role of the various healthcare professionals?

- Specialist doctor - epilepsy
- Family doctor - epilepsy
- Specialist doctor - bipolar affective disorder
- Family doctor - bipolar affective disorder
- Gynaecologist/obstetrician/nurse/midwife
- Pharmacist

What is the role of the healthcare professional? Specialist doctorepilepsy

SPECIALIST DOCTORS
prescribing valproate to girls and women of childbearing potential who suffer from EPILEPSY

APPLICABLE TO ALL THE PATIENTS: complete and sign **the annual risk acknowledgement form** (2 copies) at the start of treatment and once a year thereafter; hand over and discuss **the Patient Guide**

FIRST prescription for valproate

Only if:
- other methods of treatment are ineffective or not tolerated
- a negative pregnancy test result was obtained (in women of childbearing potential)

EXTENSION OF TREATMENT with valproate

THE PATIENT IS NOT PLANNING

Reassessment of treatment at least once

prescribing the drug to women

THE PATIENT IS PLANNING

UNPLANNED pregnancy

In epilepsy, valproate is contraindicated during pregnancy unless no other suitable method of treatment is available

It should be made clear that contraception can only be stopped after valproate has been completely

The patient should not discontinue valproate treatment and should urgently consult a specialist

Explain/remind and make sure that the patient understands the following issues

I. Risk of birth defects and neurodevelopmental disorders in children exposed to the drug **during foetal life**
II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
- even if the patient does not have a period
- continuously throughout the entire period of treatment with valproate
- regardless of sexual activity status
- refer to a contraception specialist if necessary

III. **Necessity:**
- of performing pregnancy tests if necessary during treatment
- of **planning for** pregnancy
- of **reassessment** of epilepsy treatment with a specialist doctor **once a year**

I. **Informing the patient and her partner about the risks:**
- for the foetus exposed to valproate
- concerning untreated epileptic seizures during pregnancy

II. **Explanation of the need to change the treatment if other suitable treatment method is available, and an indication that this takes time:**
- the new drug is introduced gradually, using it concurrently with valproate – it takes up to 6 weeks to reach an effective dose
- valproate is then gradually discontinued over weeks and months – usually 2-3 months

III. **If an epileptic seizure occurs during valproate discontinuation, the minimum required dose should be maintained.**

Completion and signature of the annual risk acknowledgement form at the start of treatment and during each annual visit. Handing over the Patient Guide

Applies to girls

I. The risks of birth defects and neurodevelopmental disorders should be explained to parents/guardians (and children, depending on their age).
II. The importance of contacting a specialist when a girl using valproate has her first menstrual period should be explained to parents/guardians (and children, depending on their age).
III. It is important to assess which moment would be most appropriate to give advice on contraception.
IV. The appropriateness of valproate treatment should be reassessed at least once a year.
V. Every effort should be made to change the girl's treatment to another method before she reaches adulthood.

Completion and signature of the annual risk acknowledgement form at the start of treatment and during each annual visit. Handing over the Patient Guide

If under special circumstances a pregnant patient has to take valproate because of epilepsy

Ideally, valproate should be prescribed:
- in monotherapy
- at the lowest effective dose, with the daily dose divided into several small doses
- in prolonged-release form

The patient and her partner should be referred to:
- gynaecologist/obstetrician/midwife
- specialist doctor with experience in the management of birth defects in order to initiate the appropriate monitoring of pregnancy (this includes prenatal monitoring to detect possible neural tube defects or other birth defects)

It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **should continue taking valproate and contact her specialist doctor immediately.**

FAMILY DOCTORS caring for girls and women of childbearing potential who suffer from **EPILEPSY** and are taking **valproate**

If...

THE PATIENT IS NOT PLANNING pregnancy

During each visit...

Explain/remind and make sure that the patient understands the following issues

I. **Risk of birth defects and neurodevelopmental disorders in children exposed to the drug during foetal life**
II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
- even if the patient does not have a period
- continuously throughout the entire period of treatment with valproate
- regardless of sexual activity status

III. **Necessity:**
- of performing pregnancy tests if necessary during treatment
- of **planning** pregnancy
- of **reassessment** of epilepsy treatment with her specialist doctor **once a year**

Handing over the Patient Guide

Applies to girls

I. The risks of birth defects and neurodevelopmental disorders should be explained to parents/guardians (and children, depending on their age).
II. The importance of contact with a specialist should be explained to parents/guardians (and children, depending on their age)
when a girl using valproate has her first menstrual period, so that other treatment can be considered.
III. It is important to assess which moment would be most appropriate to give advice on contraception.

It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **should continue taking valproate and contact her specialist doctor immediately.**

APPLICABLE TO ALL PATIENTS: hand over and discuss **the Patient Guide**

If ...

THE PATIENT IS PLANNING pregnancy

If there has been ...

UNPLANNED pregnancy

In patients with epilepsy, the use of valproate is contraindicated during pregnancy unless no other suitable method of treatment is

It should be made clear that contraception can only be stopped after valproate has been completely

The patient should not discontinue valproate treatment and should urgently consult her specialist doctor

I. **Informing the patient and her partner about the risks**
- for the foetus exposed to valproate
- concerning untreated epileptic seizures during pregnancy

II. **The patient should be referred to her specialist doctor immediately**
to change to another treatment if another suitable treatment is available.
III. **The patient should be advised to continue treatment with valproate until the day of the appointment to the specialist.**

Handing over the Patient Guide

The patient and her partner should be referred to:
- gynaecologist/obstetrician/midwife
- a specialist doctor experienced in the management of birth defects, for assessment and further advice

What is the role of the healthcare professional? Specialist doctor -

SPECIALIST DOCTORS
prescribing valproate to women of childbearing potential suffering from
BIPOLAR AFFECTIVE DISORDER

APPLICABLE TO ALL THE PATIENTS: complete and sign **the annual risk acknowledgement form** (2 copies) at the start of treatment and once a year thereafter; hand over and discuss **the Patient Guide**

FIRST prescription for valproate

Only if:
- other methods of treatment are ineffective or not tolerated
- a negative pregnancy test result was obtained

EXTENSION OF TREATMENT with valproate

IS NOT PLANNED pregnancy

Reassessment of treatment at least once

Change from one treatment to another before the conception

prescribing the drug to women

IS PLANNED pregnancy

UNPLANNED pregnancy

In bipolar affective disorder, the use of valproate is contraindicated during pregnancy

The patient should not discontinue valproate treatment and should urgently consult a specialist

Explain/remind and make sure that the patient understands the following issues

I. **Risk of birth defects and neurodevelopmental disorders in children exposed to the drug during foetal life**

II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
- Even if the patient does not have a period
- Continuously throughout the entire period of treatment with valproate
- Regardless of sexual activity status
- Refer to a contraception specialist if necessary

III. **Necessity:**
- of performing pregnancy tests if necessary during treatment
- of **planning for** pregnancy
- of **reassessment** of bipolar affective disorder treatment with the specialist doctor **once a year**

Completion and signing of the annual risk acknowledgement form at the start of treatment and during each annual visit
Handing over the Patient Guide

Informing the patient and her partner about the risks

- for the foetus exposed to valproate
- concerning untreated bipolar affective disorder during pregnancy

- It should be made clear that contraception can only be stopped after valproate has been completely discontinued
- Valproate should be discontinued gradually over several weeks in order to reduce the risk of early relapse[1]

- Valproate withdrawal
- Change from one treatment to another: **a rapid regimen of simultaneous decreasing the dose of the first treatment AND increasing the dose of the new treatment (so-called cross-tapering)[2] is recommended.**

The patient and her partner should be referred to:
- Gynaecologist/obstetrician/midwife
- A specialist doctor experienced in the management of birth defects in order to initiate the appropriate monitoring of pregnancy (this includes prenatal monitoring to detect possible neural tube defects or other birth defects)

Completion and signature of the annual risk acknowledgement form at the start of treatment and during each annual visit.
Handing over the Patient Guide

⚠ It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **she should continue taking valproate and contact her specialist doctor immediately.**

FAMILY DOCTORS taking care of women of childbearing potential suffering from BIPOLAR AFFECTIVE DISORDER and taking valproate

If...

IS NOT PLANNED pregnancy

During each visit...

Explain/remind and make sure that the patient understands the following issues

I. **Risk of birth defects and neurodevelopmental disorders in children exposed to valproate during foetal life**
II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
   - even if the patient does not have a period
   - continuously throughout the entire period of treatment with valproate
   - regardless of sexual activity status
III. **Necessity:**
   - of performing pregnancy tests if necessary during treatment
   - of **planning for** pregnancy
   - of **reassessment** of bipolar affective disorder treatment with her specialist doctor **once a year**

Handing over the Patient Guide

It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **she should continue taking valproate and contact her specialist doctor immediately.**

APPLICABLE TO ALL PATIENTS: hand over and discuss **the Patient Guide**

If ...

IS PLANNED pregnancy

If there has been ...

UNPLANNED pregnancy

In bipolar affective disorder, the use of valproate is contraindicated during pregnancy

It should be made clear that contraception can only be stopped after valproate has been completely discontinued

The patient should not discontinue valproate treatment and should urgently consult her specialist doctor

I. **Informing the patient and her partner about the risks**
   - for the foetus exposed to valproate
   - concerning untreated bipolar affective disorder during pregnancy
II. **The patient should be referred to her specialist doctor in order to change the treatment to another method**

Handing over the Patient Guide

The patient and her partner should be referred to:
- gynaecologist/obstetrician/midwife
- a specialist doctor experienced in the management of birth defects, for assessment and further advice

What is the role of the healthcare professional? Gynaecologist /obstetrician/nurse /midwife

GYNAECOLOGISTS, OBSTETRICIANS, NURSES, MIDWIVES caring for girls and women of childbearing potential taking **valproate**

GIRLS AND WOMEN WHO ARE NOT PREGNANT

Explain/remind and make sure that the patient understands the following issues

I. **Risk of birth defects and neurodevelopmental disorders in children exposed to the drug during foetal life**
II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
   - even if the patient does not have a period
   - continuously throughout the entire period of treatment with valproate
   - regardless of sexual activity status
III. **Necessity:**
   - of performing pregnancy tests if necessary during treatment
   - of **planning for** pregnancy
   - of **reassessment** of treatment with her specialist doctor **once a year**

Handing over the Patient Guide

It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **she should continue taking valproate and contact her specialist doctor immediately.**

APPLICABLE TO ALL PATIENTS: hand over and discuss **the Patient Guide**

In patients with epilepsy, the use of valproate is contraindicated during pregnancy unless no other suitable method of treatment is available.

In bipolar affective disorder, the use of valproate is contraindicated during pregnancy.

When a woman reports for a consultation due to **PREGNANCY WITH DRUG EXPOSURE: REFER HER TO 2 SPECIALIST DOCTORS**

Specialist doctor no. 1

A specialist in the treatment of the disease for which valproate has been prescribed, to assess and advise on changing and discontinuing the treatment if appropriate for the patient

Specialist doctor no. 2

Another specialist with experience in the management of birth defects in order to initiate appropriate monitoring of the pregnancy (this includes prenatal monitoring to detect possible neural tube defects or other birth defects) and to assess and provide advice

Handing over the Patient Guide

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

Explain/remind and make sure that the patient understands the following issues

I. **Risk of birth defects and neurodevelopmental disorders in children exposed to the drug during foetal life**
II. Mandatory use of **effective contraception** (preferably an intrauterine device or implant or two complementary forms of contraception, including a barrier method)
   • even if the patient does not have a period
   • continuously throughout the entire period of treatment with valproate
   • regardless of sexual activity status
III. **Necessity:**
   • of performing pregnancy tests if necessary during treatment
   • of **planning for** pregnancy
   • of **reassessment** of treatment with her specialist doctor **once a year.**

It should be explained that if the patient suspects she may be pregnant or becomes pregnant, **she should continue taking valproate and contact her specialist doctor immediately.**

APPLICABLE TO ALL PATIENTS: hand over and discuss **the Patient Guide**

In patients with epilepsy, the use of valproate is contraindicated during pregnancy unless no other suitable method of treatment is available.

In bipolar affective disorder, the use of valproate is contraindicated during pregnancy.

Information on educational materials

PATIENT CARD
• Ensure that it has been handed to patients
• It should be discussed each time valproate is dispensed
• The patient should be advised to keep the card

PATIENT GUIDE
• Make sure that the patient has received it

INFORMATION ONLINE
• It should be reminded that additional information is available online by scanning the **QR code** on the leaflet

3 What are the risks associated with the use of valproate during pregnancy?

The use of valproate during pregnancy is harmful to the foetus. In children exposed to valproate in foetal life, there is a high risk of:

- birth defects
- neurodevelopmental disorders

These risks are dose-dependent. There is no threshold dose below which there is no risk. Any dose of valproate taken during pregnancy may be harmful to the foetus.
The nature of the risks to children exposed to valproate during pregnancy is the same, regardless of the indication for which valproate was prescribed. Both monotherapy and polytherapy with valproate together with other antiepileptic drugs during pregnancy are often associated with abnormalities in the child.

1. Birth defects

In approximately 11%[3] of children of women with epilepsy exposed to valproate monotherapy during pregnancy, major birth defects were present.
This risk is higher than in the general population (approximately 2-3%).
The available data indicate an increased incidence of mild or severe birth defects. The most common types of birth defects:

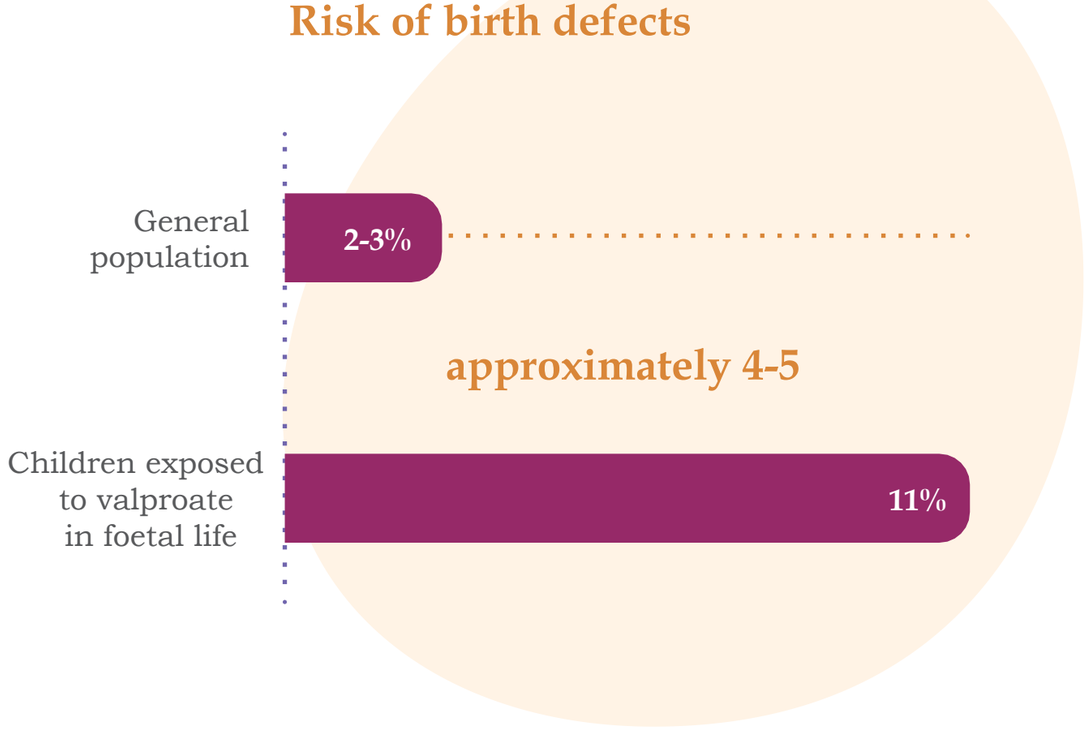
- neural tube defects
- facial dysmorphism
- cleft lip and palate
- craniostenosis
- defects of the heart, kidneys and genitourinary system

- limb defects (including bilateral radial bone aplasia)
- multiple abnormalities affecting different body systems

Exposure to valproate in foetal life may also cause the following:

- unilateral or bilateral hearing impairment or deafness which may be irreversible[4]
- congenital malformations of the eye (including eye fissures, microphthalmia) that have been reported in combination with other birth defects. These ocular malformations may affect vision.

The available data do not indicate that the use of folic acid supplements prevents birth defects associated with valproate exposure[5].



3 What are the risks associated with the use of valproate during pregnancy?

2. Neurodevelopmental disorders

- Exposure to valproate in foetal life may have a negative impact on the child's mental and physical development.

- The exact period of pregnancy during which the risk is present is not known and **it is not possible to exclude risks throughout the entire period of pregnancy.**

- Up to 30 or 40% of preschool children exposed to the drug in foetal life, may experience early developmental delays such as[6-9]:
  - later development of speech and walking skills
  - lower intellectual capacity
  - poor language skills (speaking and understanding)
  - memory problems

- In school-age children (6 years) exposed to valproate in foetal life the measured intelligence quotient was on average 7-10 points lower than in the children exposed to other antiepileptic drugs[10].
  Data on long-term effects are limited.

- Increased risk in children exposed to valproate in foetal life compared to the population without exposure:
  - attention deficit hyperactivity disorder[11]: approximately 1.5 times higher
  - autism spectrum disorders[12]: approximately 3 times higher
  - childhood autism[12]: approximately 5 times higher

The risk increased in children exposed to valproate in foetal life

Early developmental delay
Up to 30-40% of pre-school children

Intelligence
-7 to -10 points compared to children with exposure to other antiepileptic drugs

Attention deficit hyperactivity disorder with attention deficit
approximately 1.5 times higher compared to the population without exposure to the drug

Autism spectrum disorders
approximately 3 times higher compared to the population without exposure to the drug

Childhood
approximately 5 times higher compared to the population without exposure to the drug

1 What you need to know about the risks in children of fathers treated with valproate within the 3 months before the conception.

A retrospective observational study conducted in 3 European Scandinavian countries suggests an increased risk of neurodevelopmental disorders (NDDs) in children (aged 0 to 11 years) whose fathers were treated with valproate monotherapy within the 3 months prior to conception compared to children conceived by men treated with lamotrigine or levetiracetam monotherapy.

Comparison of adjusted cumulative risk of NDD in children of fathers treated with valproate within 3 months prior to conception compared to children of men treated with lamotrigine or levetiracetam

Group using valproate monotherapy — **4.0%-5.6%**

Group using lamotrigine/levetiracetam monotherapy — **2.3%-3.2%**

The pooled adjusted hazard ratio for NDDs based on meta-analysis of the datasets was 1.50 (95% confidence interval: 1.09; 2.07).

The study was not large enough to assess associations with the specific NDD subtypes assessed (the composite endpoint included autism spectrum disorders, intellectual disability, communication disorders, attention deficit hyperactivity disorder, and movement disorders). Given the limitations of the study, including the potential confounding effect of the indications and differences in follow-up time between the exposed groups, a causal relationship with valproate is possible, but it is not considered to be confirmed.

The study did not assess the risk of NDDs in the children of men who discontinued valproate treatment for more than 3 months before conception (allowing new spermatogenesis without exposure to valproate).

The observed potential risk of neurodevelopmental disorders after exposure of the father within 3 months before the conception is lower than the known risk of neurodevelopmental disorders after exposure of the mother during pregnancy.

2 What is the role of the healthcare professional in the management, treatment or care of male patients with epilepsy or bipolar affective disorder

- **It is recommended that valproate treatment should be initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar affective disorder.**

SPECIALIST DOCTOR and FAMILY DOCTOR

Explain/remind and make sure that the patient understands the following issues

I. A potential risk of neurodevelopmental disorders in children of fathers treated with valproate within the 3 months before conception.
II. The study did not assess the risk of NDDs in children of men who discontinued valproate for more than 3 months before the conception.
III. As a precautionary measure, the necessity for the following should be regularly discussed with the patient:
   - to consider **effective contraception**, including for the female partner, during valproate use and for 3 months after the treatment discontinuation;
   - to consult a specialist **in order to discuss other methods of treatment** when planning to conceive a child and before discontinuing contraception.
IV. Male patients should be advised **not to donate semen during the treatment** and for at least 3 months after the treatment completion.

The prescriber should regularly assess male patients treated with valproate to determine whether valproate remains the most appropriate method of treatment for the patient.

For male patients planning to conceive, the appropriate alternative treatment options should be considered and discussed with the patient. The individual situation should be assessed in each case.

It is advisable, if necessary, to seek advice from a specialist experienced in the treatment of <epilepsy>, <bipolar affective disorder>, <migraine>.

Handing over the Patient Guide

PHARMACIST

- Make sure that the patient has received the Patient Guide and the Patient Card
- It should be reminded that additional information is available online by scanning the QR code on the leaflet.

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BPAD: bipolar affective disorder
NDDs: neurodevelopmental disorders

COMMENTS

COMMENTS

Annual risk acknowledgement form

▼This medicinal product will be additionally monitored. This will enable new safety information to be identified quickly. Healthcare professionals are asked to report any suspected adverse reactions (see section 4.8 of the Summary of Product Characteristics).

Annual risk acknowledgement form for girls and women of childbearing age treated with valproate

Please read, complete and sign this form when you visit your specialist: at the start of your treatment, at your annual visits, and if you are planning pregnancy or becoming pregnant. This is to ensure that the patient or her legal guardian/representative have discussed with the specialist and understood the risks associated with the use of valproate during pregnancy.

Part A — To be completed and signed by

Name of the patient or her legal guardian/representative:

I confirm that the patient named above requires treatment with valproate because:

- this patient does not respond sufficiently to other drugs or ..... ☐
- this patient is intolerant to other medicines. ..... ☐

I have discussed the following information with the patient named above or her legal guardian/representative:

- The general risks for children exposed to valproate during pregnancy are: ..... ☐
  - approximately 11% risk of major birth defects and
  - 30-40% risk of developing a range of early developmental disorders that may lead to delayed psychomotor development.
- Valproate should not be used during pregnancy (except in rare cases of epileptic patients who are found to be resistant or intolerant to other drugs) and the terms of the pregnancy prevention programme should be followed. ..... ☐
- The need to have regular (at least once a year) follow-up examinations and to assess the need for continuation of valproate treatment with a specialist. ..... ☐
- The need for a negative pregnancy test result prior to the start of treatment and thereafter, according to the requirements (in patients of childbearing age) ..... ☐
- The need for continuous use of an effective method of contraception throughout the entire period of valproate treatment (in patients of childbearing age) ..... ☐
- The need to make an appointment with a doctor as soon as a pregnancy has been planned, to allow the early discussion of available treatment options and changes to other possible methods of treatments prior to getting pregnant and before discontinuation of contraception ..... ☐
- The need to contact a doctor immediately for an urgent treatment assessment in the case of suspected pregnancy or confirmation of unplanned pregnancy. ..... ☐
- I have given the patient or the legal guardian//representative a copy of the Patient Guide. More information on the use of valproate can be found at www.walproiniany.pl
- In the case of pregnancy, I confirm that this pregnant patient:
  - has received the lowest possible effective dose of valproate to minimise the possible harmful effects on the foetus ..... ☐
  - has been informed of the possibility of receiving support or counselling on pregnancy and appropriate monitoring of her child's health in the event of pregnancy ..... ☐

Name and surname of the specialist	Signature	Date

This form will be given by the specialist to girls and women of childbearing age who are being treated with valproate for epilepsy or bipolar affective disorder (or their legal guardians/ representatives).

Parts A and B of the form should be completed: all relevant boxes should be ticked and the form should be signed; this is to confirm that all risks and information associated with the use of valproate during pregnancy have been understood.

A completed and signed copy of this form will be kept/recorded by the specialist.

It is recommended that the prescribing physician saves an electronic version of the form in the patient's medical records. A completed and signed copy of this form will be given to the patient to keep.

▼ Valproate - this medicinal product will be additionally monitored. This will enable new information on the safety of the drug to be identified quickly. The user of the medicine can also help by reporting any adverse reactions that occurred after using the medicine (see section 4 of the Package Leaflet).

Annual risk acknowledgement form for girls and women of childbearing age treated with valproate

Please read, complete and sign this form when you visit your specialist: at the start of your treatment, at your annual visits, and if you are planning pregnancy or becoming pregnant. This is to ensure that the patient or her legal guardian/representative have discussed with the specialist and understood the risks associated with the use of valproate during pregnancy.

Part B To be completed and signed by the patient or legal

I have discussed with the attending specialist and understood the following information:

.....

.....

- Reasons why I require treatment with valproate instead of another drug ..... ☐
- The need to make regular (at least once a year) visits to a specialist in order to check whether valproate treatment is still the best therapeutic option in my case ..... ☐
  - Risks to children whose mothers were taking valproate during pregnancy are: ..... ☐
  - approximately 11% risk of major birth defects and
  - 30-40% risk of developing a range of early developmental disorders that may lead to delayed psychomotor development.
- The need for a negative pregnancy test result prior to the start of treatment and thereafter, according to the requirements (if I am of childbearing age) ..... ☐
- The need for continuous use of an effective method of contraception throughout the entire period of valproate treatment (if I am of childbearing age) ..... ☐

- We have discussed the possible methods of effective contraception or have scheduled a consultation with a specialist experienced in counselling on effective contraception ..... ☐
- The need to have regular (at least once a year) follow-up examinations and to assess the need for continuation of valproate treatment with a specialist ..... ☐
- The need to have a consultation with my doctor as soon as I plan to become pregnant, so that the treatment options available to me can be discussed early enough and can be changed to other possible methods of treatment before I become pregnant and before I stop using contraception ..... ☐
- The need to consult a doctor urgently if I suspect I may be pregnant. ..... ☐
- I have received a copy of the Patient Guide. More information on the use of valproate can be found at www.walproiniany.pl

In the case of pregnancy, I have discussed the following information with the attending specialist and I understand:

- the possibility to receive support or counselling on pregnancy, ... ☐
- the need for appropriate monitoring of my child's health if I become pregnant ..... ☐

Name and surname of the patient or legal guardian/representative	Signature	Date

This form will be given by the specialist to girls and women of childbearing age who are being treated with valproate for epilepsy or bipolar affective disorder (or their legal guardians/ representatives).

Parts A and B of the form should be completed: all relevant boxes should be ticked and the form should be signed; this is to confirm that all risks and information associated with the use of valproate during pregnancy have been understood.

A completed and signed copy of this form will be kept/recorded by the specialist.

It is recommended that the prescribing physician save an electronic version of the form in the patient's medical records. A completed and signed copy of this form will be given to the patient to keep.

ADR Reporting

Suspected Adverse Drug Reactions or medication errors should be reported to the Malta Medicines Authority via the ADR reporting form, available online at http://www.medicinesauthority.gov.mt/adrportal.

The ADR reporting form can be sent by post to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or via email to postlicensing.medicinesauthority@gov.mt.

Alternatively, adverse drug reactions can also be reported to Central Procurement & Supplies Unit, (Head Office),UB002, Industrial Estate, San Gwann - SGN3000 or via email: info.cpsu@gov.mt.