# An update on valproate A publication by the National Medicines Information Centre (NMIC)

Risks associated with valproate use Current risk management advice Advice for Healthcare Professionals **Educational Materials Useful Resources** 

# **Key Facts:** • There are known teratogenic and neurodevelopmental risks associated with the maternal use of

- valproate
- HPRA pharmacovigilance updates highlight the safety concerns, restrictions and contraindications associated with the prescribing and use of valproate in girls and women of childbearing potential
- Due to the potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the three months before conception, the EMA has also recommended precautionary measures for male patients • HPRA valproate risk minimisation measures are tailored to the specific responsibilities and roles of each Health Care Professional (HCP)

# countries since 1967. In Ireland, valproate is

Background

currently approved, under the brand name Epilim<sup>®</sup>, for treatment of epilepsy and for treatment of mania in bipolar disorder (when lithium is contraindicated or not tolerated).<sup>2</sup> In some cases, valproate may be the only treatment option for patients (when other treatments are ineffective or not tolerated) to maintain good seizure control and to reduce the risk of injuries from seizures and reduce mortality due to epilepsy. Valproate carries a known risk of birth defects when taken during pregnancy.<sup>2</sup> Recent figures from the UK show that valproate was prescribed

Valproate medicines have been in use in EU

to 247 patients in England during their pregnancy between April 2018 and September 2021.<sup>3</sup> In Ireland, HSE Primary Care Reimbursement Service (PCRS) data indicate that in 2023 there were over 20,435 patients in receipt of valproate on the Community Drug Schemes (CDS); with women aged between 16 and 44

accounting for 1,251 patients.4 It should be noted that these figures represent the total number of patients across all CDS and therefore may contain some double counting, where patients with a dispensing claim on multiple schemes would be counted twice. Following two EU-wide safety reviews of valproate in 2014 and 2018,<sup>5,6</sup> the Irish regulatory body, the Health Products Regulatory Authority (HPRA) issued several communications to healthcare professionals, recommending risk minimisation measures for the use of valproate in girls and women of childbearing potential.<sup>7-10</sup>

The UK regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued similar recommendations. 11 This bulletin aims to discuss the risks associated with valproate use, to outline the recent HPRA pharmacovigilance updates and to highlight the risk minimisation materials available to guide safe prescribing practices.

RISKS ASSOCIATED WITH VALPROATE USE

In Females - Teratogenic risk

committee, the Pharmacovigilance Risk Assessment Committee (PRAC). In August 2023, PRAC published an assessment report which included a review of preliminary data from an effectiveness study<sup>12</sup>

European Medicines Agency's safety

In Europe, the effectiveness of these risk

minimisation measures is monitored via the

and recommended changes to educational materials to (1) address preliminary findings and to (2) provide greater clarity on the roles of different HCPs as part of multidisciplinary care model for patients treated with Epilim<sup>®</sup>. 12 These recommendations have been incorporated into updated educational materials provided by the HPRA in Ireland. 13-18 In September 2023, a Direct Healthcare

Professional Communication (DHPC) was issued by Sanofi® (the Marketing Authorisation Holder (MAH)), and approved by HPRA, communicating an ongoing review into the risks associated with the use of valproate. 19 This was

further supported by the HPRA's Drug Safety

Newsletter in November 2023.<sup>20</sup>

More recently (January 2024) PRAC recommended precautionary measures for valproate use in **male patients**. <sup>21</sup> These precautionary measures were issued to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the three

months before conception.<sup>21</sup> The new precautionary measures for valproate use in male patients were then communicated to Irish healthcare professionals via the MAH in a HPRA approved DHPC in February 2024,<sup>22</sup> and again this was further supported by a Drug Safety Newsletter in April 2024.<sup>23</sup>

In females, both valproate monotherapy and valproate polytherapy including

early development i.e., neurodevelopmental disorders (NDDs).<sup>2,13</sup> This can present as

# valproate in utero may experience delays in their This risk is greater than in the general population

# (about 2-3%).<sup>2,13</sup>

The most common types of malformations infants being late in learning to walk and talk, include: neural tube defects, face and skull poorer speech and language skills and having a malformations e.g., 'cleft lip' and 'cleft palate', lower IQ than other children of the same age.<sup>2,13</sup> hearing impairment or deafness as well as Children exposed to valproate in utero may be malformations of the limbs, heart, kidney, urinary tract, sexual organs and of the eyes that may more likely (approximately 1.5-fold) to develop affect vision.<sup>2,24</sup> attention deficit hyperactivity disorder (ADHD)

other antiepileptics, are frequently associated with abnormal pregnancy outcomes.<sup>2</sup> Available data show an increased risk of major congenital

In Men - Paternal exposure Following a previous EU-wide review of valproate use during pregnancy, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) evaluated data from a study (EUPAS34201) conducted by pharmaceutical

conducted using secondary data from multiple registry databases in Denmark, Sweden and Norway.<sup>22,25</sup> The primary objective was to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as

monotherapy treatment, in the 3-month period

The meta-analysis of the three cohorts found a

statistically significant increased risk of NDDs,

months prior to conception, when compared to

with paternal exposure to valproate in the 3

prior to conception.<sup>22,25</sup>

lamotrigine/levetiracetam monotherapy group.<sup>22,25,26</sup> The adjusted cumulative risk of NDDs ranged from 4.0% to 5.6% in the valproate treated group versus 2.3% to 3.2% in the composite lamotrigine/ levetiracetam treated group. The 1.09 to 2.07).<sup>22,25,26</sup>

background risk was not established as an untreated group was not included as part of the study. 13,22 RECENT PHARMCOVIGILANCE UPDATES & CURRENT RISK **MANAGEMENT ADVICE** 

As part of the pharmacovigilance process, there

have been several updates reflecting the most

up time between exposure group and the

compared to the unexposed population.<sup>5,13</sup> Childhood autism is approximately 5 times more likely compared with unexposed children.<sup>2,5,13</sup>

The study also did not evaluate the risk of NDDs

Due to these study limitations, the risk of NDDs in

children of fathers that used valproate in the 3

valproate is not confirmed.<sup>22</sup> However, the **EMA** 

has recommended precautionary measures

months prior to conception is considered a potential risk and a causal association with

to children born to men who had discontinued

valproate treatment for more than 3 months

before conception (i.e., allowing a new

spermatogenesis without valproate

exposure). 13,22

for valproate use by male patients. 21-23,26 It should be noted that the potential risk associated with valproate use in men, is much lower than the estimated 30-40% risk of neurodevelopmental disorders in children born to mothers taking valproate during pregnancy. 22,27 Of interest, this safety concern about valproate use in men is under ongoing review.<sup>28</sup> PRAC has

highlighted a more recent study that does not replicate the initial retrospective observational

procedure to understand the difference in the

study findings and it has initiated a signal

findings across the studies.<sup>28</sup>

When treatment is considered necessary,

according to the Valproate Pregnancy

The PREVENT programme has been

unless the terms of a special valproate

indications (epilepsy and bipolar disorder)

1. In epilepsy, valproate is contraindicated unless

2. In bipolar disorder, valproate is contraindicated.

there is no suitable alternative treatment.

regarding use in pregnancy.

known as PREVENT.

valproate must be prescribed and dispensed

Prevention Programme, which in Ireland is

implemented nationally and across the EU since 2018.<sup>10</sup> As part of PREVENT, valproate

medicines are contraindicated i.e., must not be used, in girls and women able to have children

#### pregnancy prevention programme known as In 2014 and 2018 a number of steps were taken PREVENT are followed. to better inform women about the risks of valproate use and discourage use of valproate Of note there are differences between the two in girls and women unless there was no

pregnancy have been brought into effect. 11,13,14,21-23,27,29 In female children and women of childbearing potential, valproate (Epilim®) must be initiated

alternative. 5,6,8,10 More recently (2024-2025)

strengthened warnings and risk minimisation measures to prevent valproate exposure during

## and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Pregnancy must be excluded before treatment with valproate commences. A negative pregnancy test result in women of childbearing potential, confirmed by a healthcare provider, is required to rule out unintended use in pregnancy.<sup>2,13,14</sup>

Women of childbearing potential taking valproate

interruption for the entire duration of treatment

At least one effective method of contraception (e.g., a user independent form such as an intrauterine device or implant), or two complementary

forms of contraception including a barrier method

Individual circumstances should be evaluated in

must use effective contraception without

\_earn more

 Pregnancy planning If a woman being treated with valproate for either epilepsy or bipolar disorder is planning a pregnancy, then a specialist should be consulted prior to conception.<sup>2,13</sup> If a woman being treated with valproate for

epilepsy is planning a pregnancy, then a

treatment prior to conception and before

with valproate can be discontinued; an

before contraception is discontinued.<sup>2,13</sup>

Annual treatment reviews

contraception is discontinued.<sup>2,13</sup>

specialist must reassess the need for valproate

should be made to switch the patient to another

If a woman is being treated with valproate for bipolar disorder the specialist should be

consulted prior to conception so that treatment

alternative treatment can then be commenced

The specialist should review the patient at least

annually and decide whether valproate remains

annual risk acknowledgement form is used to help

the most suitable treatment for the patient. An

ensure that patients know and understand the

risks related to the use of valproate during

pregnancy and the need to avoid becoming

and **consider alternative therapies**. Every effort

pregnant while taking valproate. 16 The specialist should discuss the annual risk acknowledgement form at initiation and during

### Of note, oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy.<sup>2</sup> Bear the possibility of this interaction in

contraceptive advice if not using effective

contraception currently.<sup>14</sup>

In case of pregnancy

mind.30

In epilepsy, maternal tonic-clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and baby. If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for avoid high peak plasma concentrations. 7,8,13

To complement the PREVENT programme, the

professionals who manage girls and women of

Risk minimisation measures for women

treatments are ineffective or not tolerated. In

◆ valproate is contraindicated in pregnancy unless

childbearing potential, unless all the conditions of

the pregnancy prevention programme PREVENT

childbearing potential, unless all the conditions of

Similarly, the HPRA approved further guidance

regarding the potential risk of NDDs in children of

fathers treated with valproate in the three months

In male patients, it is recommended that valproate

experienced in the treatment of epilepsy or bipolar

(2024) to inform healthcare professionals

Risk minimisation measures for men

is initiated and supervised by a specialist

According to the Summary of Product

Characteristics (SmPC)<sup>2</sup> and the guide for healthcare professionals<sup>13</sup>, as a precautionary

measure, it is recommended that prescribers<sup>13</sup>:

pregnancy and in women of childbearing

potential, new contraindications apply:

there is no suitable alternative treatment.

♦ valproate is contraindicated in women of

HPRA has approved a guide for healthcare

following risk minimisation measures are

recommended 13:

In epilepsy

are met.

PREVENT are met.

before conception.<sup>13</sup>

disorder, as appropriate.<sup>2</sup>

Monitoring ▼

benefit/risk balance.<sup>2</sup>

epilepsy, it is recommended to use the lowest effective dose and divide the daily dose into at least two single doses. The use of a prolonged release formulation may be preferable to other treatment formulations in order to Patients (and their partners) with a valproate exposed pregnancy should be referred to an appropriate specialist for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects and other physical malformations. 13 Although folate supplementation before the pregnancy may reduce the risk of neural tube defects which may occur in all pregnancies, available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. 13

ADVICE FOR HEALTHCARE PROFESSIONALS

If a woman using valproate becomes pregnant or thinks that she is pregnant she should **not** stop taking

valproate. It is important that she immediately seek urgent review and be seen by a specialist to re-evaluate her

These recommendations also concern women who In bipolar disorder are not currently sexually active unless the prescriber considers that there are compelling ♦ valproate is contraindicated in pregnancy. reasons to indicate that there is no risk of pregnancy.2 ♦ valproate is contraindicated in women of

1. Inform male patients about the potential risk of NDDs in children born to men treated with valproate in the 3 months prior to conception. 2. Discuss 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.

While the approved product information i.e., the SmPC, package leaflet (PIL) and package labelling provide all the relevant valproate information, a number of recently updated educational materials are also available to provide clear information on specific risks and describe concisely what actions are required to prevent and minimise such risks. 13-18

Information on the safe prescribing of valproate

gynaecologists/obstetricians and midwives is

for various healthcare professionals including

aforementioned HPRA's guide for healthcare

The guide also outlines information for the **safe** 

Additional risk minimisation measures to further

support pharmacists in the safe dispensing of

· A pregnancy warning symbol is now visible on the

• Poster material for display in pharmacies highlights

Always use effective contraception

during your treatment with Epilim.

If you are thinking about becoming

pregnant, or if you are pregnant,

supply and counselling of both girls and women of childbearing potential and of male

For Healthcare Professionals

specialist prescribers, GPs,

professionals. 13

packaging<sup>32</sup>

risks and important actions<sup>18</sup>

for annual specialist review.

www.medicines.ie

<u>Epilepsy Ireland</u>

List button.

**Contact Us:** 

**(** 014730589

containing medicines

detailed in specific sections of the

patients treated with valproate.

valproate to patients include:

1. Development of visual aids:

suspected adverse reactions via the HPRA's online reporting service.<sup>2</sup>

Advice for Patients Comprehensive patient guides are available via the HPRA website to ensure that both female and male patients who are taking valproate are fully aware of its teratogenic and neurodevelopmental risks and the recommended safety precautions

required to minimise these risks associated with

the use of valproate. 14,15

dispensed in their original packaging whenever possible to: ensure that all patients receive a package leaflet ensure that all appropriate safety information is

to prevent broken bulk dispensing<sup>13,18</sup>

When broken bulk dispensing cannot be avoided, a

Valproate containing medicines should only be

2. Changes to dispensing practices:

#### contact your doctor urgently. WARNING FOR WOMEN Do not stop Epilim unless your AND GIRLS doctor tells you to. been identified on the outer packaging. This is to A QR code on valproate packaging and on the ensure that the information warnings contained enclosed patient information leaflet links to the elsewhere on the outer packaging are not concealed patient guide<sup>13</sup> by a dispensing label.<sup>29</sup>

Further to the guidance documents available for patients, 14,15 a patient card should be attached to the

packaging of valproate products to facilitate discussions about the risks associated with valproate use between

**USEFUL RESOURCES** 

 HPRA <u>Use of valproate-containing medicines by girls and women who can become pregnant</u> HPRA <u>Valproate guide for healthcare professionals</u> (July 2024) • HSE National Clinical Programme: <u>Valproate Pregnancy Prevention Programme</u> (PREVENT)

people and adults [NG217] (January 2025)

**EDUCATIONAL MATERIALS TO GUIDE PRESCRIBING PRACTICES** 

## and to ensure that all patients receive a package leaflet and the outer carton (which displays visual warnings) along with the patient card at each dispensing.<sup>32</sup> A best-practice location for the dispensing label has

**IMPORTANT ACTIONS FOR PHARMACISTS** 

Provide a Valproate Patient Card every time you dispense a valproate preparation and ensure that the patient understands its content.

the pharmacist and the patient each time valproate is dispensed. <sup>17</sup> Pharmacists are reminded to confirm if the patient has received a copy of the patient guide, to provide one if necessary and to remind patients of the need

# National Institute for Health and Care Excellence (NICE). NICE Guideline: <u>Epilepsies in children, young</u> • College of Sexual and Reproductive Healthcare (CoSRH) [previously the Faculty of Sexual and Reproductive Healthcare (FSRH)]. FSRH statement: Paternal exposure to valproate and the risk of neurodevelopmental disorders in children (September 2024)

- The EMA, via its risk assessment committee PRAC, continues to provide pharmacovigilance updates highlighting safety concerns with the use of valproate in girls and women of childbearing potential.
- important tools are available to help guide the safe prescribing and supply of valproate to girls and women of childbearing potential and also to males who are treated with valproate. • Not only do these educational materials support healthcare professionals in the safe and effective
- Every effort has been made to ensure that this information is correct and Reference List is prepared from the best available resources at our disposal at the time

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- malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.2 It is estimated that approximately 11% of children Although structural malformations can be the exposed to valproate in utero have major most obvious adverse pregnancy outcome, it is congenital malformations at birth. 2,3,5-11,13,14 known that up to 30 - 40% of children exposed to

Available evidence does not show that folate supplementation prevents birth defects due to valproate exposure. 13

companies of valproate containing products. 22,23,25 This retrospective observational study was

pooled adjusted hazard ratio was 1.50 (95% CI: Therefore, around 5 children in every 100 had NDDs when born to fathers treated with valproate compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam. 15 The study was not large enough to investigate

associations with specific NDD subtypes and did have a number of limitations including: potential confounding by indication, differences in follow-

recent valproate safety concerns. prevent valproate pregnancy prevention programme PREVENT Programme

Additional key elements of the PREVENT programme (full details can be found via the

the EMA <sup>8,10</sup> as follows:

Pregnancy test

Contraception

with valproate.<sup>2</sup>

should be used.<sup>2,13</sup>

HPRA website) include recommendations from

### each case and the patient should be fully involved in the discussion regarding the method of contraception chosen, to guarantee her engagement and compliance with the chosen measures. The patient should be referred for

each annual review with the patient, and should ensure that the patient has understood its content.<sup>2,13,14</sup> A copy of the signed risk acknowledgement form should be filed in the patient's medical record and a copy should be provided to both the patient and her GP.<sup>16</sup>

treatment with valproate and to consider alternative treatment options.<sup>2,13,14</sup>

childbearing potential treated with valproate. 13 The management of epilepsy or bipolar disorder. 3. Healthcare professionals should prescribe and dispense valproate according to the PREVENT programme. 1. Valproate should not be used in female children 4. For women of childbearing potential who are and women of childbearing potential unless other currently using valproate, specialists should

2. In female children and women of childbearing

supervised by a specialist experienced in the

regularly re-evaluate treatment to ensure that the

are met and that valproate remains the most

5. Prescribers should discuss the risk with their

patients and ensure that patients understand the

appropriate therapeutic option for them.

conditions associated with the PREVENT

understand the patient guide.

programme. Patients should also receive and

conditions of the pregnancy prevention programme

potential valproate must be initiated and

## considered and discussed with the patient. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate. 5. Male patients should be advised **not to donate**

sperm during treatment and for at least three

6. Provide patients with the HPRA-approved

months after treatment discontinuation.

patient guide.

3. Regularly review treatment in male patients to

4. For male patients planning to conceive a child,

suitable alternative treatment options should be

evaluate whether valproate remains the most

suitable treatment for the patient.

• In the European Union (EU), medicines that are being monitored particularly closely by regulatory authorities are labelled with a black inverted triangle (▼) in the product information. 31 Additional monitoring aims to enhance reporting of suspected adverse drug reactions.<sup>31</sup> Valproate is subject to this additional monitoring (▼) which will allow for the continued monitoring of the • Healthcare professionals are reminded to report any pregnancy exposures and any associated

Learn more about HPRA reporting

## copy of the package leaflet should always be provided with a warning sticker added.<sup>32</sup> The pack size of valproate containing medicines (Epilim<sup>®</sup>) has been reduced to mitigate against the need for broken bulk dispensing at the pharmacy level

visible

 Remind patients of the risks of birth defects/neurodevelopmental disorder valproate in pregnancy and reinforce the need for effective contraception If a woman of childbearing potential reports that she is not taking effective contraception, refer her to her GP. Dispense valproate in the original packaging with the outer carton warning text and symbol. Where repackaging cannot be avoided always provide a copy of the package leaflet and a patient card and add a warning sticker to the bag into which the blisters Ask if the patient has received a Valproate Patient Guide and provide a copy if necessary. Remind patients of the need for annual specialist review.

 Summary of Product Characteristics (SmPC), licenced product information. Available at <u>hpra.ie</u> and • Health Products Regulatory Authority (HPRA) Precautionary measures for male patients using valproate-

# <u>European Medicines Agency</u> (EMA) • Organisation Anticonvulsant Syndromes Ireland (OACS) • Best Use of Medicines in Pregnancy (BUMPS)

- Summary: • There are known teratogenic and neurodevelopmental risks associated with the parental use of
- More recently, the EMA has recommended precautionary measures for the treatment of male patients; this is due to the potential increased risk of NDDs in children born to men treated with valproate during the three months before conception. • The HPRA has approved updated guidance to reflect this information and as a result, a number of
  - prescribing of valproate, the materials can be used to help ensure patients are fully informed of the risks of use and are better able to discuss options with their care providers.

Please let us know what you think of our Bulletin!

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of issue. Our full list of references can be accessed via the Reference