



Medicines & Healthcare products  
Regulatory Agency

# **Valproate: review of safety data and expert advice on management of risks**

**Public Assessment Report**

Medicines and Healthcare products Regulatory Agency  
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# 1. Plain Language Summary

## Key messages:

Valproate (as sodium valproate, valproate semisodium, or valproic acid; brand names Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo and Dyzantil) is approved in the UK to treat epilepsy and bipolar disorder. It is also sometimes used outside of the licence ('off label') to treat other conditions.

Valproate can cause serious harm to an unborn baby if it is taken during pregnancy. Due to these risks, it has been advised for some time that valproate should only be used in female children or in any woman able to have children (women of childbearing potential) if other treatments do not work (ineffective) or are not tolerated. If valproate is used in women of childbearing potential then the conditions of the Pregnancy Prevention Programme need to be followed. The Pregnancy Prevention Programme is designed to make sure patients are fully aware of the risks of valproate and agree to take steps to avoid becoming pregnant while taking this medicine.

In light of concerns that the regulatory requirements for safe use of valproate were not being consistently followed, particularly that pregnancies continued to be exposed to valproate, and emerging data on the risk of harms in male patients, the MHRA conducted a review of the available data and asked for advice from the independent Commission on Human Medicines (CHM), which also listened to the views of patients and healthcare professionals.

The CHM advised that the current measures to reduce the risk of harm to patients and their children should be strengthened. The CHM advised that no one under the age of 55 should be initiated on valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment. The CHM also advised that for existing patients, 2 specialists should independently consider and document that there is no other effective or tolerated treatment or that the risks do not apply to that individual patient. The full recommendations from the CHM are included in this report, as well as the information they considered. The MHRA communicated this information to the UK public and to healthcare professionals in December 2022.

After their review, the CHM formed an implementation group to advise on the safe introduction of the new measures into clinical practice. The implementation group, which includes experts and representatives from across the healthcare system, advised that the measures should be introduced in a phased way to ensure ongoing patient care is not disrupted. The implementation group proposed that the measures should apply firstly to all new patients under 55 years old and women already under specialist review. This is because the level of reproductive risks is greatest for women of childbearing potential. This advice

was considered by the CHM who accepted it. Updates are now being made to information for healthcare professionals and patients about valproate. New educational materials will be released in January 2024. Further information on the implementation of the new safety measures was communicated to the public and healthcare providers in November 2023.

A second phase of regulatory action is planned, this will take into account the impact of the initial phase and will also be informed by an ongoing re-analysis of data on risks to children of male patients taking valproate. The MHRA has communicated on the [ongoing re-analysis](#) and also issued [advice to healthcare professionals](#). More details will follow in 2024.

No-one should stop valproate without advice from their healthcare professional. Any patient who thinks they are pregnant while on valproate should be advised to talk to their healthcare professional urgently.

### **Introduction to this report**

The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The CHM advises government ministers on the safety, efficacy and quality of medicines.

This report presents the review of the safety data by the MHRA in 2022, the advice of the CHM and the implementation group in 2022 and 2023, and the steps that the MHRA are taking to implement new safety measures with the support of patients and experts.

### **More information about valproate**

Valproate is a medicine used in the management of epilepsy and in bipolar disorder. Epilepsy is a medical condition that affects the brain generally leading to a tendency to have seizures. There are many different types of epilepsy, which can have different causes. People with bipolar disorder experience periods of depression (feeling very low and lethargic) and mania (feeling very high and overactive), and often a mixture of these. The high and low phases of bipolar disorder often interfere with everyday life and there are options for treating bipolar disorder that can help with minimising these.

Due to the known risks of valproate in pregnancy, a number of measures have been taken to reduce the risk of a developing baby being exposed to this medicine. In 2018 the valproate Pregnancy Prevention Programme was introduced following a review by the MHRA and across Europe. See [Drug Safety Update from April 2018](#) for more information.

During the 2018 review, a number of concerns were also considered about risks in all patient groups, not only women of childbearing potential, and these included the potential risks to

babies born to fathers who take valproate (paternal risks), as well as the possible effects of valproate being passed down through more than one generation (intergenerational or transgenerational effects). European studies were started to provide further data on paternal risks and any intergenerational or transgenerational effects of valproate. More information on the 2018 review is available in the [summary from the European Medicines Agency](#).

### **Reasons for this review and information considered**

At the time of the review, information on the use of valproate in England showed that the number of pregnant women prescribed valproate in a 6-month period had fallen from 68 women in April to September 2018, to 17 women in October 2021 to March 2022. These babies have an 11% risk of birth defects and a 30 to 40% risk of neurodevelopmental disabilities, which can be permanent. In light of concerns that the current regulatory requirements for safe use were not being consistently followed, the MHRA conducted a review of the available data.

The review also considered data for other potential risks, including that, as indicated in the current product information, valproate may impair male fertility, for which there is some evidence that this is reversible upon discontinuation. In addition, data were considered from studies in juvenile rats and adult rats and dogs reporting adverse effects to the male reproductive system in animals receiving valproate, as well as non-clinical studies on the potential for epigenetic effects of valproate and transgenerational risks. The CHM was also concerned about the prescribing of valproate outside of its authorised uses.

The MHRA reviewed the risks and presented options on how best to minimise harm to the UK public. This review is presented in this report, alongside the advice and how the MHRA took on their feedback.

### **A summary of how the CHM reached their conclusions**

Over a series of meetings, the CHM considered information summarised by the MHRA on risks linked to valproate medicines, including information from the lived experience of patients, data from a registry of valproate prescribing in England, and published studies in humans and published and unpublished data in animals. The CHM also considered information presented by the MHRA about the numbers of patients in the UK taking valproate and how this has changed over the years.

In coming to its advice, the CHM heard directly from experts, stakeholders, and patient groups on how valproate was being used and how the existing regulatory measures have impacted on the use of valproate.

## Conclusions of the review

The CHM noted from the MHRA assessment that some pregnancies continue to be exposed to valproate despite the significant risks and current pregnancy prevention measures. The CHM also considered some evidence from studies in animals that effects on behaviour linked to valproate could be passed on through more than one generation.

The CHM also discussed evidence from the MHRA assessment relating to the risk of impaired fertility in male patients on valproate. The CHM noted evidence that the possible risks of a father on valproate transmitting harm to a baby are under study, and that some non-clinical data have shown toxic effects to the testes of animals being given valproate in studies, with uncertain implications for the developing male reproductive system in humans.

Evidence provided directly to CHM from patient support groups and from stakeholders showed that compliance with the Pregnancy Prevention Programme is a concern and some women on valproate are still not informed about the risks by their healthcare professionals.

## Recommendations of the CHM

The CHM therefore recommended that more should be done to minimise the risks of valproate. The CHM advised on further risk minimisation measures. The CHM's advice is presented in [section 15](#).

The CHM recommended that no patients (male or female) under the age of 55 years should be initiated on valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment. For patients under 55 years already taking valproate, the CHM recommended that 2 specialists should agree there is no other effective or tolerated treatment if valproate is to be continued.

These measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme. These measures also aim to reduce initiation of valproate to only in patients for whom no other therapeutic options are suitable.

The CHM advised that these measures should apply to people under the age of 55 because this is the age group most likely to be affected by the risks of valproate in pregnancy and the risk of impaired fertility in males. However, the risks should also be considered when prescribing to men and women over the age of 55 years planning to have children.

Other measures recommended by CHM include improved educational materials and better monitoring of healthcare professionals' compliance with the new measures.

Information was provided to the [public](#) and to [healthcare professionals](#) on the recommended measures in December 2022.

## Implementation advice for the CHM recommendations

Following their review, the CHM established an implementation group to advise on the safe introduction of the new measures into clinical practice. This group was formed of clinicians, experts, and representatives from the UK healthcare system. The group met several times in 2022 and 2023 to give their advice.

The CHM considered feedback from the implementation group and other stakeholders on the measures. They advised on a phased implementation of the requirements to ensure that they could be introduced safely and effectively. They advised that implementation should begin with new patients considering starting valproate and girls and women under 55 already on valproate who should already be receiving annual specialist reviews. They also advised on the proposed process for the second specialist to give oversight, who would meet the definition of specialist, and on the educational materials to support these new measures for patients and healthcare professionals. This is considered to be a risk proportionate approach.

The MHRA also worked with patients and their representatives on messages in the updated educational materials to support patients on valproate and help them to understand the risks.

The MHRA continues to review any new data on the risks of valproate. This includes potential risks for children of men taking valproate. In August 2023 we published a [statement](#) and an [update for healthcare professionals](#) on this ongoing review. The revised study analysis will be carefully re-assessed by the MHRA and any further guidance will be communicated to patients and healthcare professionals as soon as possible.

A second phase of regulatory action is planned for 2024, this will take into account the impact of the implementation of the initial phase and the ongoing evaluation of the risks associated with valproate. More details will follow in 2024.

### Next steps for the public

If you are a patient on valproate, please discuss any concerns you have with your healthcare professional. No one should stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may become worse without treatment, which can be harmful.

On 28 November 2023 we issued an [alert asking health organisations to prepare now for these new measures to reduce ongoing serious harms of valproate](#). Please see [the MHRA's collection of information and guidance](#) on the reproductive risks of valproate and new safety measures introduced to reduce these risks.



## 2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines. Public Assessment Reports relating to previous reviews of valproate were published by the European Medicines Agency in [October 2014](#) and [February 2018](#).

This report presents the MHRA's review of safety data for valproate in 2022 and expert advice on management of risks recommended by the CHM over multiple meetings. This report also presents the advice from the CHM's implementation Expert Working Group, which met several times in 2022 and 2023 and the changes their advice made to the introduction of these regulatory safety measures.

We have made changes to the ordering and wording used in the original assessment reports to aid readability and to add context. The initial consideration of the study evaluating the risks to children whose fathers had taken valproate when they were conceived has not been included within this report, as this data is subject to re-analysis.

A [glossary](#) is provided for an explanation of the terms used in this report.

The assessments contained in this report reflect evidence that was available at the time of the review in 2022. The MHRA and the CHM continues to monitor the safety and usage of valproate closely and will issue further reports, if required, as further analyses become available.

## **3. Background**

### **3.1 Pharmacological properties**

Valproic acid was synthesised as a derivative of valeric acid. It was mainly used as a solvent for organic compounds until the 1960s, when it was discovered to have anticonvulsant properties.

The active ingredients in the authorised medicines are either sodium valproate, valproic acid or valproate semisodium. Valproate semisodium, is a stable coordination compound comprised of sodium valproate and valproic acid in a 1 to 1 molar relationship. It is also known as divalproex sodium. The term valproate is used throughout this report to cover all of these active ingredients.

The most likely mode of action for valproate is thought to be potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the synthesis or metabolism of GABA. Valproate may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels, which has the effect of reducing excessive electrical activity in the brain.

### **3.2 Initial authorisation of valproate in the UK**

The first application for valproate was received by the marketing authority which at the time was the Department for Health and Social Security (DHSS), in 1971, and considered by the Committee of Safety of Medicines (CSM). In January 1972, the CSM Sub-Committee on Toxicity and Clinical Trials reported that clinical studies of sodium valproate did not show adequate evidence of safety and efficacy, and further toxicological and teratological data was required. After requesting further clinical data, in May the same year, they concluded that they were unable to advise granting the licence, due to inadequate data on toxicology and teratology. Specifically, they raised concerns about this data “in view of the expected long term administration of the drug”. The following month, the Sub-Committee reported that they had received sufficient data to grant a conditional licence for a year, limiting sodium valproate use to hospitals and other specialist centres for epilepsy, provided all patients were monitored for therapeutic efficacy and safety, and the results reported to the licensing authority.

### 3.3 Harms in pregnancy

Since the general marketing of valproate in 1974, the product information for doctors has included a warning about the possible risk of birth defects after in-utero exposure (in pregnancy). Further data subsequently demonstrated that in-utero exposure to valproate can seriously affect the brain development of a child, which may become more apparent as they grow up. As the risks to unborn children have been increasingly understood, the regulatory warnings have been strengthened. A timeline is available outlining [the regulatory history relating to use of valproate in pregnancy](#).

As noted in the current Summary of Product Characteristics (SmPC) for valproate, a meta-analysis (including registries and cohort studies) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations (Weston and others, 2016). This is greater than the risk of major malformations in the general population (approximately 2–3%). Studies in children exposed in-utero to valproate show that up to 30–40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems (Bromley and others, 2010; Cummings and others, 2011; Meador and others, 2009; and Thomas and others, 2008).

The MHRA has kept the risks of valproate in pregnancy under review, both nationally and when part of the European medicines regulatory network in the European Union (EU). The CHM has continued to advise on the strengthening of risk minimisation measures for valproate and further monitoring of its use for women of childbearing potential.

In 2018, following a safety review across Europe, a Pregnancy Prevention Programme was introduced with the aim to rapidly reduce the number of pregnancy exposures to valproate and to eventually eliminate prescribing in pregnancy.

Safety concerns about the use of valproate during pregnancy were a key focus of the [Independent Medicines and Medical Devices Safety Review](#). There are ongoing concerns raised by patients and patient support groups that the current risk minimisation measures have not been sufficient and more stringent measures were needed to prevent the serious harms of valproate in pregnancy.

### **3.4 Initiation of the 2022 CHM review**

In May 2022, the MHRA sought advice from the CHM following the release of data showing continued prescribing of valproate during pregnancy in England. Although use in female patients has declined 30% since 2018, the data show a plateauing of this decline in prescribing in the [March 2022 report of the Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England](#). In September 2021, there were 20,192 prescriptions for valproate in women, of which 206 were issued to female patients newly starting valproate compared to 195 in September 2020. It was noted that despite the introduction of the Pregnancy Prevention Programme there were still prescriptions of valproate being issued in the same month that a pregnancy was recorded. In addition, it was noted there was prescribing of valproate outside of the terms of its licence for prevention of migraine and in mental health conditions other than bipolar disorder (Paton and others, 2022).

### **3.5 Assessments considered by CHM**

The CHM considered the presented evidence of continued exposure of pregnancies to valproate in England and views of patients and their representatives at meetings in May and June 2022 on the adequacy of existing risk minimisation measures, in the context of additional safety signals under evaluation.

These safety signals included:

- review of the published mechanistic evidence for the mode of action of valproate including reported epigenetic effects and histone deacetylase inhibitory properties
- updates on the risk of valproate-associated testicular toxicity in juvenile and adult animals and the uncertain clinical relevance to the male paediatric population
- consideration of the known risks of infertility in adult male patients
- pre-clinical data showing inter-generational and transgenerational effects of valproate as well as published data from a French charity survey reporting intergenerational effects of valproate in humans
- the potential for harm to children born to fathers taking valproate

The CHM recommended that more stringent risk minimisation measures were warranted. The CHM advised the clinical circumstances around the exposed

pregnancies which had been identified, despite the Pregnancy Prevention Programme, should be explored wherever possible to further understand the decision-making process. Patient details are anonymised within the [Medicines and Pregnancy Registry](#) but following data protection procedures and permission, the MHRA were able to discuss the circumstances surrounding a selection of the cases with prescribers directly, to establish whether there were any specific aspects of the Pregnancy Prevention Programme that were failing.

The Clinical Practice Research Datalink was interrogated to provide an overview of prescribing of valproate in different patient populations in the UK.

In addition, further data were gathered to inform the CHM's considerations including seeking the views of stakeholders. The CHM listened closely to all of the evidence provided by experts, stakeholders, and patient groups and asked questions to understand more about each perspective. These views were an important part of the evidence considered by the CHM in making their recommendations.

Further information on the international patterns of valproate prescribing received from the Marketing Authorisation Holders and from other regulators was also considered by the CHM.

This report presents a summary of the evidence considered by the CHM. The CHM was asked to advise whether the new and emerging evidence changed the benefit-risk profile of valproate in any population and whether the current risk minimisation measures were sufficient. The CHM was asked to advise on a range of additional risk minimisation options and whether these should apply to all patient populations taking into account the licensed indications (epilepsy and bipolar disorder).

This report includes the full recommendations of the CHM and the considerations of the Valproate Implementation Expert Working Group and the Valproate Stakeholder Network.

## 4. Indication and clinical information about valproate

Valproate is a medicine that is authorised to manage the symptoms of epilepsy and is also authorised in the UK for the treatment of bipolar disorder. It is used outside of its licence to treat a number of other conditions including migraine, which is a licensed indication in some other countries.

The licensed indication for the brand leader product Epilim (sodium valproate) at the time of the 2022 review was for the ‘treatment of generalized, partial or other epilepsy’. The brand leader for bipolar disorder is Depakote (valproate semisodium), which was indicated at the time of the 2022 review for the ‘treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated’, with the indication noting it can also be considered for the continuation of treatment after manic episode in patients who have responded to Depakote for acute mania.

Several Marketing Authorisation Holders have both the epilepsy and bipolar disorder indications in the same branded product (for example Episenta and Epival).

In a previous EU review in 2014 co-led by the UK and Netherlands (see [publication of European Medicines Agency in 2014](#)), the efficacy of valproate as well as the mechanism of action was re-assessed, in the context of the benefits and risks assessment. It was concluded that valproate is considered to be an effective drug in the treatment of epilepsy and of manic episodes in bipolar disorder, which are serious conditions that might be life-threatening if not adequately controlled. Based on clinical data and on the views of the relevant experts, at that time, it was considered that valproate should remain an option for female children and women of childbearing potential but specialists were asked to only use it when other treatments are ineffective or not tolerated. This strengthened the previous advice not to prescribe valproate without specialist neurological advice and only if the benefits of its use outweighed the risks. Following this review, the warnings on the risks of valproate use in pregnancy and need for contraception were also strengthened and the MHRA [communicated this to healthcare professionals in January 2015](#).

## 4.1 Treatment of generalised and focal epilepsy

The Joint Task Force with European Academy of Neurology (Tomson and others, 2015) recommends that, where possible, valproate prescribing should be avoided in women of childbearing potential and that every female patient and the parents of a female child must be fully informed of the risks associated with valproate use during pregnancy as well as of the risks and benefits of other treatments.

The guideline from Tomson and colleagues (2015) states that valproate may be offered as a first line treatment for some epilepsy syndromes where it is considered the most effective treatment, including idiopathic (genetic) generalised syndromes associated with tonic-clonic seizures. Further, they emphasise that situations exist (where the woman has failed to respond to other treatment alternatives or the risks of withdrawal are not acceptable) where it is appropriate to prescribe valproate to women of childbearing potential.

For focal epilepsies, there are a number of other treatments with either superior or similar efficacy. Therefore, the guideline states that valproate should not be initiated as a first-line treatment.

For the management of genetic generalised epilepsy (GGE), for some patients for whom other treatments have failed, valproate may be the only therapeutic option, including pregnant women or women of childbearing potential. Gesche and colleagues (2017) suggest that about 20% of GGE patients who are drug resistant or have refractory seizures became seizure free when treated with valproate. Considering that GGE accounts for 15 to 20% of epilepsies and that 16 to 36% of GGE patients are drug resistant, the proportion of patients with epilepsy who may only respond to valproate may be small.

Other licensed monotherapy treatment options for primary generalised tonic-clonic seizures (GTCS), mainly in the context of GGE, are lamotrigine, phenobarbital, phenytoin and topiramate. These treatments may also be used in combination therapy.

However, it is known that not every patient responds to these other treatment options, and other therapies including valproate may be considered. Phenobarbital and phenytoin may not be appropriate to treat GTCS, as use of these products can result in poor seizure control and increase the risk of injury or epilepsy-related death (Tomson and others, 2015).

In 2021 the MHRA published outcomes from the [comprehensive safety review](#) of available safety data relating to the use of other key antiepileptic drugs (AED) in pregnancy for the risk of major congenital malformations, neurodevelopmental disorders and delay, and other effects on the baby. Based on these findings, other AEDs (or antiseizure medicines), such as lamotrigine and levetiracetam were not associated with an increased risk of birth defects compared with the general population and so were considered by CHM to be safer for the baby than valproate if used during pregnancy.

Considering its risks, since the time of first authorisation, valproate has not been licensed for first-line treatment in women of childbearing potential and valproate is contraindicated in pregnancy unless there is no other suitable treatment. The risk of seizures due to discontinuation or switch of AEDs, including valproate, seems to be higher during pregnancy and loss of seizure control in pregnancy is associated with severe consequences including maternal and fetal death.

For this reason, in line with current recommendations in the [valproate product information](#), if a patient is planning to become pregnant, withdrawal of valproate or a switch to another treatment should always be considered following a timely discussion with the physician to assess the benefits and risks for the patient. Treatment changes should be completed and adequately evaluated before conception. For valproate, as well as for other treatments, the lowest effective dose should be established before conception.

## **4.2 Treatment of manic episodes in bipolar disorder**

At the time of the review, valproate was indicated for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. Valproate is not indicated as maintenance treatment for manic-episode-free bipolar disorder only. As such, the indication noted that continuation of treatment after the manic episode can be considered in patients who have responded to valproate for acute mania. Clinical guidance advises that other treatments options are atypical antipsychotics or electroconvulsive therapy (ECT).

Based on the current data, the existence of a group of patients who may only respond to valproate for the treatment of bipolar disorder is not established. Alternative treatments include the antipsychotics aripiprazole, quetiapine, risperidone and olanzapine, the product information for which notes some extent of reproductive toxicity in animal studies. However, due to limited information, the risk in human pregnancy of these drugs is unknown.



All antipsychotics may cause adverse drug reactions in new-born infants when exposed during the third trimester, including extrapyramidal and/or withdrawal symptoms.

Electroconvulsive therapy (ECT) and direct-current cardioversion do not seem to pose a significant risk to the fetus. Following a recently published systematic literature review regarding the use of ECT in pregnancy (Leiknes and others, 2015), the most frequent adverse effect of ECT in the mother was premature contractions and labour (28%), whereas in the fetus it was bradyarrhythmia (43%).

For valproate, the current product information for bipolar disorder provides largely the same precautions and warnings as for epilepsy for women of childbearing potential. The valproate product information states it should not be used unless other treatments are ineffective or not tolerated and that women of childbearing potential should use effective contraceptive measures in line with the Pregnancy Prevention Programme. However, valproate is contraindicated in pregnancy for those with bipolar disorder, whereas the product information for the management of epilepsy states it is contraindicated in pregnancy unless there is no other suitable treatment. The distinction is made based on the lack of a clearly identifiable group of patients with bipolar disorder who only respond to valproate, whereas the group of patients with epilepsy who might only respond to valproate has been more clearly identified and includes those people with genetic generalised epilepsy.

Results of a study (part one of the Caisse Nationale d'Assurance Maladie des Travailleurs Salaries (CNAMTS) study) conducted in France showed the majority of pregnant women receiving valproate for the treatment of bipolar disorders switch or discontinue this therapy early during pregnancy (mostly in the first trimester) (EMA assessment report, 2018). This provides evidence that, for bipolar disorder, successful switching away from valproate is possible. For the management of bipolar disorder, several other medications are available with lower known reproductive risks and good evidence of efficacy such as the newer generation antipsychotics. The Royal College of Psychiatrists has a position statement to help guide prescribers (see section 4.4).

### **4.3 Prophylaxis of migraine**

Valproate is not authorised for use in the prophylaxis of migraine in the UK, however, it is known to be prescribed in the UK for this use, which is outside the terms of its licence.

### **4.4 Switching from valproate to other medicines**

#### **4.4.1. Guidance for epilepsy**

The Task Force of the European Academy of Neurology provides recommendations based on expert opinion for switching from valproate to other treatments in women of childbearing potential (Toledo and others, 2020). According to this recommendation, the switch of valproate to another treatment will commonly occur over at least 2 to 3 months. The new medication is usually introduced as an add-on to valproate until a potentially effective dose of the second drug has been achieved and after this, an attempt can be made to gradually taper down and discontinue valproate.

In the UK, no single specific clinical guidance document is adopted for the clinical management of switching from valproate during pregnancy or to provide clear guidance on clinical criteria for considering switching medications. It is acknowledged that switching from valproate during pregnancy is a very challenging clinical issue and individual patients require a tailored approach. It is acknowledged that valproate discontinuation during pregnancy might not always be possible.

#### **4.4.2. Guidance for bipolar disorder**

In 2018 the Royal College of Psychiatrists issued a position statement on the [withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness.](#)

#### **4.4.3. Future studies**

An EU switching study is being conducted by Marketing Authorisation Holders involving the UK Clinical Practice Research Datalink and a French database. Results are expected at the end of 2023 at the earliest. This switching study aims to identify best practice when discontinuing or switching from valproate by stratifying using all relevant factors in both indications.

## 5. Risks of valproate in pregnancy

Valproate is a known teratogenic medicine, resulting in both physical birth defects and neurological disorders, some of which may lead to permanent disability.

The SmPCs for valproate products state that a meta-analysis (including registries and cohort studies) (Weston and others, 2016) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3%). Studies in children exposed in-utero to valproate show that up to 30–40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

The risk of major congenital malformations (see next section for further details) in children after in-utero exposure to AED polytherapy including valproate is higher than that of AED polytherapy not including valproate.

This risk is highly dose-dependent with valproate monotherapy, and available data suggests it is dose-dependent with valproate polytherapy (Tomson and others, 2015). However, a threshold dose below which no risk exists cannot be established.

The current review did not consider any new data on the magnitude and nature of congenital abnormalities or neurological disorders in children of women who took valproate in pregnancy. However, it did include a summary of evidence for the risks in pregnancy, as well as data for risks with other AEDs.

Valproate crosses the placenta freely (Semczuk-Sikora and others, 2010). The risk of structural malformations is greatest in the first trimester; however the risk of neurodevelopmental harm is thought to be present throughout all three trimesters. There is therefore no established safe period of exposure.

The group of features caused by structural malformation and neurodevelopmental harm in children who have been exposed to valproate in-utero is referred to as 'Fetal Valproate Spectrum Disorder' (Clayton-Smith and others, 2019; Bromley and others, 2019). It is listed on [Orphanet](#) with prevalence unknown and International Classification of Diseases 10 code Q86.8. The term Fetal Valproate

Syndrome is also used although this does not adequately reflect the associated neurological disorders.

The [MHRA introduced a Pregnancy Prevention Programme](#) in 2018 to support the regulatory position that the balance of benefits and risks of valproate is negative for girls and women of childbearing potential, unless other treatments are ineffective or not tolerated. The Pregnancy Prevention Programme involves annual review and the requirement for highly effective methods of contraception (such as a hormonal intrauterine device).

## **5.1 Magnitude and type of birth abnormalities**

In terms of the magnitude of risk, data derived from a meta-analysis (including registries and cohort studies) (Meador and others, 2008) reported that 10.73% of children of women with epilepsy exposed to valproate monotherapy during pregnancy have congenital malformations (95% confidence interval (CI) 8.16 to 13.29). This is a greater risk of major malformations than for the general population, where the risk is about 2% to 3%.

In terms of the type of birth abnormalities, available data shows an increased incidence of both minor and major malformations in children born to mothers treated with valproate during pregnancy. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Most recently, data from case reports has shown a clear link with valproate exposure and hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

In-utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Further research is needed to fully document the prevalence of harm in the children exposed to valproate in utero and to fully characterise all signs and symptoms which form part of the Fetal Valproate Spectrum Disorder.

## **5.2 Dose dependency of the risk of major congenital malformations**

The risk is highly dose dependent. The frequency of major congenital malformations in one study was shown to be 24% at doses at or above 1,500 milligram per day in monotherapy (Tomson and others, 2015). A lowest dose threshold below which no risk exists cannot be established. The incidence of harm is reported to be higher with valproate than with other AEDs including lamotrigine, levetiracetam and carbamazepine (Weston and others, 2016).

In a second study from Tomson and colleagues the frequency of birth defects was shown to be increased to 25.2% (95% CI 17.6 to 34.2) ([Tomson and others, 2018. Table 3](#)) with valproate monotherapy. Even at the lowest dose category (over 650 milligram per day), valproate was associated with a significantly greater risk of birth defects than most other treatments.

In line with the results from Meador and colleagues, in 2018 Tomson and colleagues, reported the risk of birth defects (defined as structural abnormalities with surgical, medical, functional, or cosmetic importance, and classified according to the 2005 EUROCAT criteria) following valproate exposure as 10.3% (95% CI 8.8 to 12.0) and also reported clear dose-dependent effects.

## **5.3 Magnitude and type of risks of neurological harm**

Studies in preschool children exposed in utero to valproate show that up to 30% to 40% of children experience delays in their early development such as talking and walking later and other neurological disabilities including lower intellectual abilities, poor language skills (speaking and understanding) and memory problems (Thomas and others, 2008; Meador and others, 2009; Bromley and others, 2010; Cummings and others, 2011).

Intelligence quotient (IQ) measured in school-aged children (age 6 years) with a history of valproate exposure in-utero was on average 7 to 10 points lower than those children exposed to other AEDs (Meador and others, 2009). Although the role of confounding factors cannot be excluded, there is evidence that in children

exposed to valproate, the risk of intellectual impairment is independent from maternal IQ.

Available data show that children exposed to valproate in-utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population (Christensen and others, 2013).

Available data from another population-based study (Christensen and others, 2019) show that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

The risk of neurodevelopmental disorders (including that of autism) has been reported to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists cannot be established based on available data (Tomson and others, 2015). When valproate is administered in polytherapy with other AEDs during pregnancy, the risks of neurodevelopmental disorders in the offspring were also significantly increased compared to those in children from the general population or born to untreated women with epilepsy.

#### **5.4 Risk of miscarriage (spontaneous abortion)**

A Danish study by Bech and colleagues (2014) showed an increased risk of spontaneous abortion especially if women with epilepsy used high doses of valproate (over 750 milligrams per day), clonazepam (over 4 milligrams per day) and carbamazepine (over 500 milligrams per day). There is conflicting evidence around the background risk of spontaneous abortion and stillbirth in women with epilepsy and a high background rate in the general population. In addition, data capture is difficult for early miscarriages that do not require hospital in patient or day case care.

Bech and colleagues reported that after adjusting for potential confounders, pregnant women using all AEDs had a 13% higher risk of spontaneous abortion than pregnant women not using AEDs (adjusted risk ratio 1.13, 95% CI 1.04 to 1.24). However, the risk of spontaneous abortion was only increased in those women using an AED without a diagnosis of epilepsy (aRR 1.30, CI 1.14 to 1.49) and was not increased in women using AEDs with an epilepsy diagnosis (aRR 0.98, CI 0.87 to 1.09). The authors concluded that unmeasured confounding may explain the slight increased risk for spontaneous abortion with any AED use

(among women both with and without epilepsy). They found no association between AED use during pregnancy and stillbirth, but the statistical precision of the analysis was low.

The currently available data do not provide robust evidence of an increased risk of spontaneous abortion, low birth weight, or premature delivery following exposure to valproate during pregnancy. However, these specific pregnancy outcomes have not been formally assessed during the current review.

## **5.5 Risks of valproate compared to other AEDs**

A large nationwide cohort study provides information on the risks of early neurodevelopmental disorders associated with in-utero exposure to valproate and the other main AEDs currently used (Coste and others, 2020).

Firstly, the study reports a 4 to 5 fold higher risk of early neurodevelopmental disorders following exposure to valproate, more specifically concerning pervasive developmental disorders, “mental retardation” (term reflects terminology used by study authors Coste and colleagues, 2020) and disorders of psychological development. Exposure to valproate was found to have a dose-response relationship with occurrence of neurodevelopmental disorders and also had a different impact according to the period of exposure: children exposed during the second and/or third trimesters of pregnancy had a markedly increased risk of early neurodevelopmental disorders, unlike children exposed to valproate only during the first trimester.

Secondly, the study reported that the risk of neurodevelopmental disorders associated with other AEDs was much lower than that associated with valproate. The slight increases in the risk of several mental and behavioural disorders with lamotrigine and carbamazepine were no longer observed when the analysis was confined to children born to a mother with no known mental illness, suggesting an effect of maternal mental illness or associated characteristics rather than exposure to these drugs.

In multivariable analysis, children exposed to valproate, compared to unexposed children, were at higher risk of NDs (aHR, 3.7; 95% CI 2.8–4.9)—especially pervasive developmental disorders (aHR, 4.6; 95% CI 2.9–7.5), disorders of psychological development (aHR, 4.7; 95% CI 3.5–6.4) and mental retardation (term used by study authors; aHR, 5.1; 95% CI 3.1–8.5)—and utilisation of speech therapy (aHR, 1.7; 95% CI 1.4–2.1). These estimates were similar or

higher among children born to a mother with no known mental illness. Comparison with children exposed to lamotrigine showed three to fourfold increased risks of pervasive developmental disorders, mental retardation (term used by study authors) and disorders of psychological development with valproate (Coste and others, 2020).

The associations observed between pregabalin and phenobarbital and “mental retardation” (term reflects terminology used by study authors Coste and colleagues, 2020), behavioural and emotional disorders, and utilisation of orthoptic services were based on limited or very limited sample sizes. For the other AEDs, either no increased risk in disorders was observed (clonazepam or gabapentin) or only associations with increased health care use in specific areas (oxcarbazepine, levetiracetam, topiramate), often at the limit of significance ([Coste and others, 2020](#)).

The CHM previously advised on a [comprehensive safety review](#) of available data relating to the use of other key AEDs in pregnancy for the risk of major congenital malformations, neurodevelopmental disorders and delay, and other effects on the baby. The review concluded that the risk of neurodevelopmental delay with carbamazepine, lamotrigine, and levetiracetam is much lower than with valproate or was not increased from background rate, although an increased risk cannot be definitively ruled out.

## **5.6 Summary of the potential mechanisms for valproate toxicity in pregnancy**

Although valproate is established to be a highly teratogenic medicine, the mechanism underpinning this effect is not yet established and teratogenic expression of valproate exposure is likely multifactorial.

There is evidence from the published literature that valproate can affect epigenetic marks and chromatin structure through inhibition of class I histone deacetylases (HDACs), which favour histone acetylation, especially at the lysine 9 residue of histone H3 and the lysine 8 residue of histone H4 (Mello and other 2021; [Göttlicher and others, 2001](#); [Phiel and others, 2001](#); [Eyal and others, 2004](#)).

Valproate inhibition of HDACs is reported in the literature by some investigators to be the principal way in which the teratogenicity of the drug is mediated (Finnell R and others, 2021). This inhibition results from the binding to the catalytic centre



which restricts substrate access, resulting in a hyper-acetylation of the N-terminal tails of histones H3 and H4 in vitro and in vivo. Inhibition of HDAC results in an overall increase in gene expression. Using *Xenopus* and zebrafish as model organisms, Finnell and colleagues found that valproate exposure increased neural patterning and cardiac malformations.

Interaction of valproate with folate metabolism has long been suspected of underlying valproate's teratogenicity and this hypothesis is among the best characterised to date. It has been established that plasma folate and methionine levels are significantly reduced upon valproate treatment, accompanied by an increase in homocysteine and tetrahydrofolate levels. When valproate treatment is accompanied by folate supplementation, the exencephaly rates decreased by 50% in both mice and rats. (Finnell and others, 2021). In humans, although it is known that folic acid intake can reduce (background risk) of neural tube defects by 50%, there is no evidence that this is effective in preventing valproate-induced neural tube defects (Jentink and others, 2010; Ban and others, 2015).

There is evidence in the literature that valproate has modulatory effects on a large number of cellular pathways, which underlie its efficacy in neurological disorders but also provide biological mechanisms for its side effects. Beyond the enhancement of GABA-mediated neurotransmission, valproate is a sodium and calcium channel inhibitor, has been found to affect signalling systems like the Wnt/beta-catenin and ERK pathways and to interfere with inositol and arachidonate metabolism. Valproate treatment also produces marked alterations in the expression of multiple genes, many of which are involved in transcription regulation, cell survival, ion homeostasis, cytoskeletal modifications and signal transduction. In addition, valproate enhances activator protein-1 DNA binding and there is evidence from the literature of histone deacetylase inhibitory properties (Rosenberg and others, 2007).

Valproate is a widely utilised pharmacological tool for neuro-epigenetic research (Chen and others, 2012). Most likely, both immediate biochemical and longer-term genomic influences underlie the effects of valproate in its indications and associated side effects (Rosenberg and others, 2007). As a result of the pleiotropic effects of valproate, the focus of regulatory action has been on minimising harm via other mechanisms such as the Pregnancy Prevention Programme in addition to continuing research identifying specific risk factors for harm. The impact of valproate on the HDAC enzyme is under evaluation by another expert working group of the CHM.

Being a simple natural fatty acid, valproate is a substrate for the fatty acid oxidation pathway, which primarily occurs in mitochondria (Silva and others, 2008). As detailed in several studies (Labbe and others, 2008; Fromenty and others, 1997), valproate impairs mitochondrial function via several mechanisms, which can be briefly summarised as inhibiting mitochondrial fatty acid oxidation through the sequestration of coenzyme A (a cofactor mandatory for fatty acid oxidation), and also possibly by an electrophilic metabolite of valproate inactivating  $\beta$ -oxidation enzymes. In addition, valproate can induce opening of mitochondrial permeability transition pores, which may explain why valproate-induced microvesicular steatosis is associated with liver cell death.

In a literature overview forming part of the EU Pharmacovigilance Risk Assessment Committee (PRAC) assessment in [2017-2018](#) regarding effects on mitochondria, known side effects were described such as liver toxicity, Reyes-like syndrome, pancreatitis and immune deficiency (leukopenia). However, there is no clear evidence that mitochondrial dysfunction caused by valproate is associated with the development of autism.

The [European PRAC](#) in 2018 concluded that the currently available data do not warrant further investigation regarding the potential association between mitochondrial dysfunction and autism. Valproate is however contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase- $\gamma$  (POLG), such as Alpers-Huttenlocher Syndrome, and in children under 2 years of age who are suspected of having a polymerase gamma (POLG) related disorder.

## **5.7 Maternal risks of uncontrolled epilepsy in pregnancy**

In the [2020 Maternal, Newborn and Infant Clinical Outcome Review Programme \(MBRRACE\)-UK report of Confidential Enquiries into Maternal Deaths and Morbidity between 2016 and 2018](#), it was noted that neurological causes (epilepsy and stroke) were the second most common indirect cause of maternal death, and the third most common cause of death overall. There was a statistically significant increase in maternal mortality due to sudden unexpected death in epilepsy (SUDEP), with 22 women who died during or up to a year after the end of pregnancy in the UK and Ireland in 2016 to 2018 from causes related to epilepsy. In 2017 to 2019 the [2021 MBRRACE-UK report](#) states that 18 women died from SUDEP during or up to a year after the end of pregnancy. The report

provides information relating to risk factors for the cases of SUDEP but does not provide details of how they relate to the drugs prescribed at the time of death.

The need to balance the fetal risk from valproate against the maternal risk of death from uncontrolled epilepsy was summarised in the subsequent 2021 MBRRACE-UK report as follows:

*‘The MBRRACE-UK team, working together with the charity SUDEP Action, have been invited to present to several groups, including the All-Party Parliamentary Group on Epilepsy, to try to ensure that women’s needs are recognised alongside those of fetal wellbeing.’*

It is essential therefore that any clinical guidance also ensures that women receive effective AEDs to manage their epilepsy, receive periconception counselling so they are offered a suitable therapeutic for their situation, and are supported to continue taking their medicines during pregnancy.

In terms of alternatives to valproate, the [CHM’s review published January 2021](#) concluded that lamotrigine (brand name Lamictal) and levetiracetam (brand name Keppra) are two AEDs with the largest body of evidence showing no increased risk of birth abnormalities compared with the general population. The available information also did not suggest an increased risk of the child having difficulties with learning or thinking ability. However, further data are needed to draw firm conclusions on neurodevelopmental outcomes.

## **6. Risks of valproate in male patients**

### **6.1 Summary of male risks**

Much of the previous regulatory action for valproate has focused on reproductive risks in women and the risk to the fetus via in-utero exposure. Less information is available regarding reproductive risk in male patients; however reproductive risks in males remains an area of concern.

The European review in 2017 focussed on the risks of valproate related to maternal exposure. It recognised that there was an unknown risk to the fetus from paternal exposure but that preclinical data suggested the risk of autism spectrum disorder like phenotype was transmitted through some of the male animals to the third generation in those animals born to mothers who hadn't been exposed to valproate (Choi and others, 2016).

The European PRAC review in 2018 considered the available evidence for a link between human fathers taking valproate and the risk of congenital malformations in their children and the risk of developmental disorders and concluded that while the weighted cumulative evidence was insufficient at that time to support or rule out a causal association between valproate and reported observations in children exposed to valproate via their father, further studies were needed.

The marketing authorisation holders for valproate were required, as a condition of their licence, to perform a retrospective study to evaluate the possible association between paternal exposure to valproate and the risk of congenital abnormalities and neurodevelopmental disorders including autism spectrum disorders in offspring. It was also recommended that additional nonclinical studies need to be performed to evaluate the possible impact of valproate on genome and epigenome of germ cells (such as mutagenicity, clastogenicity and gene expression).

The risks of impaired fertility or male infertility have been included in the valproate SmPCs since 2011. More recently in 2021, advice was updated to reflect that a limited number of case reports suggest that a dose reduction may improve fertility function. However, it is noted that in some cases, the reversibility of male infertility was unknown. The UK valproate SmPC also lists some adverse effects relating to abnormal hormonal balance in terms of hyperandrogenism (hirsutism, virilism,

acne, male pattern alopecia, and/or androgen increase) as uncommon adverse events and gynaecomastia as very rare.

The non-clinical section of the product information approved by the US Food and Drug Administration (the regulator in the USA) has contained information about testicular toxicity in juvenile animals for some time. In August 2021 and April 2022, the CHM reviewed preclinical data on the impact of valproate on the juvenile testes of animals and more widely on the male reproductive tract following prenatal and adult exposures (Choi and others, 2016; Conei and others, 2021a; Conei and others, 2021b; Källén 2008; Tartaglione and others, 2019; Cansu and others, 2011; Cohn and others, 1982; Krogenaes and others, 2008; Snyder and Badura, 1995; Bairy and others, 2010; Iamsaard and others, 2017; Ibi and others, 2019; Khan and others, 2011; Nishimura and others, 2000; Ourique G and others, 2016; Soliman and others, 1999; Sveberg Røste and others, 2001; Sveberg Røste and others, 2002; Tanabe and others, 2021; Vijay and others 2008). Based on this data, the CHM previously advised that the valproate SmPC should reflect the totality of the non-clinical data from the published literature and from studies performed by the brand leader which have shown testicular toxicity in adult rats and dogs and juvenile rats.

The CHM and the Paediatric Medicines Expert Advisory Group previously considered the clinical relevance of the non-clinical data reporting effects on the developing and mature testes, and the male hormone production role of the testes. The relevance of the testicular toxicity data in juvenile animals exposed to valproate for the paediatric male population is uncertain and further studies were recommended.

There is currently information in section 5.3 of the SmPC about the risks of behavioural abnormalities in first generation offspring of mice and rats after in-utero exposure (see [Section 7](#) on Transgenerational risks). Some behavioural changes transmitted by male (and female) mice, who had been prenatally exposed to valproate and mated with valproate-naive (unexposed) females (or males) have also been observed in the second and third generation offspring (see [Section 7](#) on Transgenerational risks).

Behavioural changes were less pronounced in the third generation of mice following acute in-utero exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

## 6.2 Preclinical Juvenile Testicular Toxicity

The current SmPC for all valproate-containing medicines already includes a statement on fertility in male patients. The SmPC for Epilim includes the following warning:

‘Valproate administration may also impair fertility in men. Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.’

The mechanism of infertility has not been established.

Two unpublished studies in juvenile rats identified the immature testis as a target organ of toxicity for valproate, with an effect (–54% and –40% reduction in mean absolute testicular weights and mean relative testicular weights in neonatal and immature rats respectively) consistent with reductions in testicular weights reported in both adult rats and dogs (unpublished data). The toxicological significance and clinical relevance of the testicular findings in juvenile rats was reviewed to determine whether there also was a potential risk of adverse effects arising from exposures during childhood and adolescence. Published studies on the effect of valproate on juvenile testicular development and more widely on the effect of valproate on the testes from prenatal through to adult exposures were considered (Choi and others, 2016; Conei and others, 2021a; Conei and others, 2021b; Källén 2008; Tartaglione and others, 2019; Cansu and others, 2011; Cohn and others, 1982; Krogenaes and others, 2008; Snyder and Badura, 1995; Bairy and others, 2010; Iamsaard and others, 2017; Ibi and others, 2019; Khan and others, 2011; Nishimura and others, 2000; Ourique G and others, 2016; Soliman and others, 1999; Sveberg Røste and others, 2001; Sveberg Røste and others, 2002; Tanabe and others, 2021; Vijay and others 2008).

The toxicological properties of valproate have been characterised in a large number of marketing authorisation holder-sponsored studies and published studies performed in various species (mice, rats, guinea pigs, rabbits, dogs, goats) via the oral, intravenous, intraperitoneal and subcutaneous routes of administration at doses high enough to induce toxicity in the animals. The age of some of these studies pre-date the requirements for the current standards for toxicity testing. However, the more recent Good Laboratory Practice (GLP)-

compliant studies, as well as the large numbers of published studies characterising the toxicity of valproic acid, confirm the effects reported in the original studies.

The main toxicological effects identified included teratogenicity, central nervous system (CNS)-related neurological signs (including sedation, ataxia, tremors), reduced body weights and bodyweight gain, which may be a central effect of valproate, reticuloendothelial and lymphoid tissue lesions, as well as reduced spermatogenesis and testicular atrophy at doses higher than the non-toxic oral doses of 50mg/kg/day in the mouse, 200 mg/kg/day in the rat and 90 mg/kg/day in the dog.

There are extensive data demonstrating the testicular toxicity of valproate in sexually mature animals. The testicular changes reported include reductions in mean absolute and relative testes weight, spermatogenetic arrest at various stages of germ cell development and increased apoptosis, degeneration of the seminiferous epithelium and testicular atrophy. Changes in sperm parameters consist of reduced sperm counts, abnormal morphology and motility, as well as sperm DNA fragmentation. The toxicity is dose- and duration-related. Changes in mating behaviour indicative of effects on sexual function and infertility have been reported in the literature (Bairy and others, 2010; Iamsaard and others, 2017; Ibi and others, 2019; Khan and others, 2011; Nishimura and others, 2000; Ourique G and others, 2016; Soliman and others, 1999; Sveberg Røste and others, 2001; Sveberg Røste and others, 2002; Tanabe and others, 2021; Vijay and others 2008).

The plasma concentrations associated with the testicular weight reductions in the juvenile and adult pre-clinical studies were not measured, therefore the relationship between the plasma concentrations associated with these adverse effects and plasma concentrations achieved in patients are not known. Estimates based on pharmacokinetic data extrapolated from other studies indicates that there may be no safety margin for the reductions in testicular weights reported at 240mg/kg in the juvenile and adult rats following intravenous administration.

The clinical relevance of the findings of preclinical studies in male animals was first evaluated by the CHM in April 2020 and it was agreed that this potential risk should be further investigated. At a meeting of CHM in August 2021, it was agreed that the product information should be updated and a further clinical study

on the effects of valproate on the endocrine and reproductive function of males was required.

These findings were considered again in 2022 as part of this review since they added to the concerns about the safety of valproate in male patients.

### **6.3 Adult male fertility**

Information about the possible adverse effects on male fertility are currently included in section 4.6 and 4.8 of the SmPC (sections concerning fertility, pregnancy and lactation and undesirable effects, respectively) following spontaneous reports in male patients. Reports of impaired male fertility have been received through the UK suspected adverse reaction reporting system (Yellow Card scheme) and similar schemes run by international regulators. The mechanism of infertility in male patients is not known at present.

Section 4.6 of the Epilim SmPC states that valproate administration may impair fertility in men and that fertility dysfunctions has been reported in some cases to be reversible at least 3 months after treatment discontinuation. It also notes a limited number of case reports and literature (Tallon and others, 2021) suggest that a “strong” dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was not reported.

### **6.4 Possibility of teratogenic risk through paternal exposure to valproate**

Questions were raised at a public hearing held by the European Medicines Agency in 2017 by patients and stakeholders about whether the teratogenic risk can be transmitted following paternal exposure to valproate (in other words, can a child be affected through a father taking valproate).

In 2013, the impact of in-utero exposure to AEDs and child development at 18 and 36 months was investigated using data entered from mid-1999 to December 2008 in the prospective Norwegian Mother and Child Cohort study (Veiby and others, 2013). In this study, as a second objective, development in children of fathers with epilepsy was examined (Veiby and others, 2013).

A total of 363 children had a father with reported epilepsy, of which 37% were treated with an AED at any time during the 6 months preceding conception and were followed for at least 18 months (table 2 in Veiby and others, 2013). The



study did not distinguish between the different AEDs, therefore, there were no specific results for valproate. However, children of fathers with epilepsy treated with an AED had a significantly greater risk of adverse development scores for tests of personal social skills (odds ratio (OR) 2.3, (95% CI 1.3 to 4.1) and a measure of autistic traits (OR 3.7 (95% CI 1.4 to 10.1)) at 18 months of age compared with children whose fathers had epilepsy but were untreated. No differences in gross or fine motor skills were observed between groups. No statistically significant increase in risk was found for any of the outcomes measured at 36 months.

The authors considered that this study did not provide evidence of a causal association between paternal exposure to AEDs and adverse child development in children with fathers who have epilepsy but noted limitations in the findings due to small sample size.

In 2013, Engeland and colleagues performed a cohort study that linked two population-based registries, the Medical Birth Registry of Norway and the Norwegian Prescription Database. The study cohort consisted of 340,000 pregnancies from 2004 to 2010. The study did not identify paternal drug exposure in the 3 months prior to conception as an important risk factor for adverse pregnancy outcomes but information on the fathers of pregnancies terminated due to birth defects or health problems in the child (n=1285) were not recorded.

As an output of the 2018 EU review, a retrospective study is ongoing on this potential risk using real world data from Sweden, Denmark and Norway, with a final report due in 2023.

After the completion of this review in 2022, the results of this retrospective post authorisation safety study evaluating the paternal risk of valproate were received by the MHRA in 2023. The study report submitted to the MHRA and to other regulatory authorities suggested an increased risk of neurodevelopmental disorders in children whose fathers took valproate during the 3-month period before they were conceived compared to children whose fathers had taken the antiseizure medicines lamotrigine or levetiracetam. However, MHRA were subsequently informed of errors in the study that may impact on the results. The revised study analysis will be carefully re-assessed by the MHRA and any further guidance will be communicated to patients and healthcare professionals as soon as possible.

## 7. Transgenerational risk

Concerns have been raised by patients and stakeholders about whether the teratogenic risk or the risk of neurodevelopmental disorders can be transmitted through more than one generation. The available data on transgenerational risks associated with valproate were considered by the [EU PRAC in their 2018 review](#).

Since March 2020, the current Epilim SmPC has included the following information in the preclinical section (section 5.3) reflecting the currently available data from the studies by Choi and others (2016) and Tartaglione and others (2018):

*“Behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute in utero exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.”*

These data along with new studies and analysis were considered in this review.

Publications suggest that valproate is able to induce altered DNA methylation (Houtepen and others, 2016), by acting as a HDAC inhibitor (Phiel and others, 2001; Kubota and others, 2012).

Jia and colleagues (2015) demonstrated that a change in gene expression in male mice after exposure to a HDAC inhibitor was also observed in the offspring of these mice. In experiments in *Xenopus* embryos, Phiel and colleagues (2001) found that valproate and a well characterised HDAC inhibitor (trichostatin A) were teratogenic, whereas non-teratogenic analogues of valproate did not inhibit HDAC.

Choi and colleagues (2016) observed transgenerational transmission of autism-like symptoms and increased expression of excitatory postsynaptic proteins in the first, second and the third-generation offspring (F1, F2 and F3) of mice administered a single dose of valproate during pregnancy (F0). The study investigated the transmission of effects via the male germline (male offspring) and

showed the paternal transmission of effects to the third generation. A symptom of teratogenicity was also observed in the F1 (first generation) offspring (crooked tail, considered a mild form of neural tube defect) but not in the F2 and F3 (second and third generation respectively) offspring. Limitations of the study included the small group size (6 dams per group) and only one dose was used and the functional consequences of the effect on the proteins were not clear.

Overall, the number of tests performed and the consistency of effects up to the F3 generation suggest some transgenerational effect of valproate on the investigated autism-like symptoms and proteins.

At the time of the review, studies commissioned after the 2018 European referral were awaited. These studies focus on potential epigenetic effects and the potential transgenerational risk for valproate.

## 8. Safety of valproate in older patients

Not all patient populations are at the same risk of the adverse effects of valproate in pregnancy and of male fertility. Therefore, it is important to consider the use of valproate in populations where the currently identified harms of valproate are of less or no relevance. The review considered safety data for older patients.

At time of this review, the SmPC provided little information on specific issues relating to safety or efficacy in the elderly. However, it does state that that, although the pharmacokinetics of valproate are modified in the elderly, this is associated with “limited clinical significance” and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In general, fertility declines with age. As such clinical advice for women at age 55 and above is that all women can cease contraception as spontaneous conception after this age is exceptionally rare, even in women still experiencing menstrual bleeding ([Faculty of Sexual and Reproductive Health. Contraception for Women Aged over 40 Years, August 2017, amended July 2023](#)).

Data from the Clinical Practice Research Datalink (CPRD) in people over 55 years shows similar use of valproate in men and women with a slight decline in new prescriptions. Valproate use in older people is reported to be in line with the rest of the exposed population, with epilepsy being the most common indication and valproate use as a mood stabiliser second in frequency of use to epilepsy.

Estimates of the absolute number of patients prescribed valproate in the period September to December 2021 have been based on the estimated rates from CPRD extrapolated using an estimate of the UK population (estimated based on ONS population data 2010-2020 as 2021 data were not yet available). The estimated numbers of patients by age and sex prescribed, and newly prescribed, valproate in September to December 2011 are presented below.

**Table 1: Estimated number of patients (in 1000's) prescribed valproate in the UK in September to December 2021**

Prescribing	Sex	Age group				
		0-11 years	12-15 years	16-44 years	45-54 years	55+ years
<b>All patients prescribed</b>	Female	2.3	0.7	9.1	13.4	44.0
	Male	5.5	2.8	34.6	19.8	44.3
<b>New starters</b>	Female	0.1	<0.1	0.1	0.1	0.6
	Male	0.4	0.2	0.8	0.3	0.5

Switching frail adults stable on valproate to other agents may lead to adverse outcomes such as seizure recurrence and falls, which may lead to a fracture and poorer outcome and is not justified based on the absence of reproductive risks.

## 9. Current risk minimisation measures

The review considered the effectiveness of the risk minimisation measures in place for valproate medicines in the UK at the time of the review.

### 9.1 Pregnancy Prevention Programme

In April 2018, healthcare professionals were informed of [new restrictions to valproate-containing medicines for girls and women of childbearing potential](#). The Pregnancy Prevention Programme included the requirement for an annual specialist review for all women of childbearing potential on valproate.

This was in addition to the existing position that valproate should only be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder and that treatment in female girls and women of childbearing potential should only be initiated if other treatments are ineffective or not tolerated.

Within the Pregnancy Prevention Programme annual review, all female patients should complete an Annual Risk Acknowledgement Form (ARAF). In addition it was recommended that a patient reminder card and updated patient and healthcare professional educational materials should be disseminated, and a visual warning should be added to the outer packaging of the dispensing boxes. These materials are intended to keep the risk of valproate in pregnancy constantly at the forefront in the ongoing risk assessment of healthcare professionals and patients.

### 9.2 England Antiepileptics in Pregnancy Registry

In 2021 and 2022, the MHRA funded NHS Digital to develop the [Medicines and Pregnancy Registry](#). This work builds towards the recommendation from the Independent Medicines and Medical Devices Safety Review (IMMDSR) that a UK registry to include all women on AEDs who become pregnant should be developed.

The first report of the registry which focussed on valproate was published in February 2021. Reports have been published bi-annually with the report considered by the CHM in March 2022 the first to also cover all AED and with analyses presented in dashboard form. The registry is based on the linkage of

routine community dispensing, hospital admission, and maternity services data already held by NHS Digital for England only. Healthcare professionals do not proactively enter their patients for the registry.

### **9.3 Ensuring women receive information on the risks**

Between 1 November and 13 December 2021, the Department of Health and Social Care (DHSC) and Medicines and Healthcare products Regulatory Agency (MHRA) consulted on proposals to enable original pack dispensing (OPD) and whole-pack dispensing of medicines containing valproate in community pharmacies across the UK.

The aim of these measures is to increase patient safety by ensuring the medicine is provided with the patient information leaflet (PIL), which contains information about the safe and effective use of a product.

The consultation included a proposal that medicines containing valproate will always be dispensed to the nearest whole pack (either up or down) to ensure that patients receive the manufacturers' specific and unique warnings and pictograms, including a patient card and the statutory PIL (in the whole pack), which alert patients to the risks to unborn children.

Following a [consultation](#), the Government amended the Human Medicines Regulations 2012 (HMRs) to:

- require manufacturer's original full pack dispensing of valproate-containing medicines
- enable pharmacists to supply up to 10% more than or less than the amount on a prescription of medicines other than those containing valproate, so that they can dispense a manufacturer's original full pack instead of splitting the pack, known as original pack dispensing (OPD).

The change came into force in England, Scotland and Wales from 11 October 2023. The legislative changes do not currently apply to Northern Ireland. The MHRA issued [guidance](#) on the reasons for the change to dispensing of valproate-containing medicines, and outlined what pharmacists need to do differently. This guidance on dispensing valproate-containing medicines should be considered by pharmacists in Northern Ireland as good practice.

## 9.4 Patient and Healthcare Communications

In April 2018, the Chief Medical Officers (CMO) of the UK wrote to all healthcare professionals to inform them that [valproate was contraindicated in women of childbearing age unless they met the conditions of the Pregnancy Prevention Programme](#).

In Summer 2021, NHS England and Improvement wrote to all women of childbearing potential that were taking valproate. The [letter](#) detailed the risks that are associated with valproate and the requirement to be on effective contraception. In addition, the letter highlighted the need for an annual review of treatment.

Regulatory communications to reduce and finally eliminate the risks of valproate have been informed by feedback from the Valproate Stakeholders Network (VSN). Introduction of strengthened measures was supported by wider communication efforts via members of the VSN and through standard channels such as its safety bulletin Drug Safety Update ([10 articles](#) have been published since the initiation of the first EU review of neurological disorders associated with valproate up to the time of this review).

In response to ongoing evidence of non-compliance with the Pregnancy Prevention Programme from patient organisations the MHRA has:

- Published further articles in Drug Safety Update to remind healthcare professionals of their responsibilities ([September 2018](#) and [December 2018](#))
- Circulated [a letter to pharmacists through Central Alerting System signed by Chief Pharmaceutical Officers](#) (22 October 2018)
- Liaised with the General Pharmaceutical Council and Pharmaceutical Society Northern Ireland to contact registered pharmacists
- Added a Quality Improvement Data standard on prescribing of valproate to patients of childbearing potential for GP practices in Clinical Practice Research Datalink

The MHRA has also worked with the professional bodies (including the General Medical Council, General Pharmaceutical Council, Care Quality Commission) and bodies (such as the Royal College of General Practitioners, Association of British Neurologists, Royal College of Psychiatry) in efforts to achieve compliance with the conditions of the Pregnancy Prevention Programme.



In addition, GP electronic system providers have provided a 'search and audit' function to facilitate the identification of women of childbearing age on valproate and have updated the software alerts.

The UK is included in several ongoing post-authorisation safety studies being conducted by a consortium of Marketing Authorisation Holders across Europe using data from a variety of EU member states to explore best practice guidance for switching from valproate to other AEDs and better characterisation of Fetal Valproate Spectrum Disorder. The UK CPRD is part of the EU drug utilisation study monitoring the impact of the Pregnancy Prevention Programme on valproate use in women of childbearing age and the compliance with conditions of the Pregnancy Prevention Programme, which [reported in March 2023](#). The MHRA will monitor the findings of these studies closely and, where appropriate, take action promptly.

# 10. Analysis of effectiveness of current risk minimisation measures

An analysis was done on the effectiveness of risk minimisation measures in place for valproate at the time of the review.

## 10.1 Detailed data from Antiepileptics in Pregnancy Registry

Data considered by the CHM from the March 2022 report of the [Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England](#), covering from 1 April 2018 to 30 Sep 2021\* showed that:

- Around 20,000 females in this age group were dispensed a prescription of valproate in England each month
- 8,000 of these were females aged 16-44 years and the registry showed that the rate of declining use of valproate in this age group was slowing
- 53 pregnancies with likely exposure to valproate had occurred in the most recent year of the data.

In the complete registry, in the 42-month period from April 2018 to September 2021, 49,599 women between the ages of 0 and 54 years were prescribed and dispensed valproate by the NHS at least once.

At the time of the review, there had been a reduction of only 7,256 in the number of women aged 0 to 54 prescribed valproate on a monthly basis over the time period of the registry, from 27,448 in April 2018 to 20,192 in September 2021 – see [March 2022 Registry report](#).

The initial fall in prescribing seen in 2018 and early 2019 appeared to have plateaued later in 2019: with a 10.4% decline in the number of women prescribed valproate from 27,455 in April 2018 to 24,589 in March 2019 compared to a decline of 1.6% (23,934 to 23,555) from April 2019 to March 2020.

A decline in the number of women starting valproate was seen in mid-2020 however, again, the rate had plateaued. Of the 20,192 women aged 0-54 years

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\* Further data have been added retrospectively to the registry since this report which were not previously available so numbers may have altered slightly.

prescribed valproate in September 2021, 206 were not prescribed valproate in the previous 12 months, and therefore classed as “new starters”. This compares to 195 “new starters” in September 2020.

Of the 206 female new starters on valproate under the age of 54 years in September 2021, 45 were aged 0 to 11 years, 4 were aged 12 to 15 years, 82 were aged 16 to 44 years, and 75 were aged 45 to 54 years.

Of the 20,192 women in the registry prescribed valproate in the March 2022 report, 832 had an identified pregnancy conceived since April 2018. However, only 247 women out of these 832 women were prescribed valproate in a month in which they were pregnant. From April to September 2021, 100 women became pregnant having previously stopped valproate; similar figures were seen in previous reporting periods. This suggests an impact of the risk minimisation approaches in that a significant proportion of women stopped taking valproate prior to pregnancy.

It is notable that of the 832 female patients on the register at the time of the March 2022 report who had a record of conception since April 2018, 613 had a pregnancy in which they did not receive valproate. Of these, 505 female patients on the register stopped receiving prescriptions for valproate prior to a pregnancy and did not restart after pregnancy, within the reporting period. This suggests that these women were switched successfully onto other AEDs.

The majority of these women stopped valproate more than 12 months before conception. Table 2 shows the AEDs the women were prescribed during their pregnancy.

**Table 2: List of antiepileptic drugs (AEDs) prescribed for those female patients who stopped valproate prior to pregnancy**

From March 2022 report of the [Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England.](#)

<b>AEDs</b>	<b>Female patients (number)</b>
Another AED (not listed below)	53
An antipsychotic	116
Carbamazepine	13
Gabapentin	11
Lamotrigine	105
Levetiracetam	152
Oxcarbazepine	3
Phenobarbital	1
Phenytoin	3
Pregabalin	16
Topiramate	6
Valproate	0
Zonisamide	13

It is notable that in this report, of the 247 women prescribed valproate in the month in which they were pregnant, 117 were on monotherapy, defined as not receiving a prescription for another AED in that same month. The remainder were prescribed one (97 women), two (28 women) or three (5 women) other AEDs, suggesting use of these medicines for a drug-resistant epilepsy. It is notable that several AEDs can limit the effectiveness of hormonal contraceptives, highlighting the need for detailed contraceptive advice.

In the March 2022 report, of the 247 female patients prescribed valproate in the month in which they were pregnant (reflecting 259 pregnancies), over 50% were prescribed valproate only during the first trimester and then stopped, while 38%

were prescribed during the first trimester and continued. The remainder received their first prescription after the first trimester or during the delivery month. Stopping valproate in the first trimester or starting it in the second or third may represent a misunderstanding of the time window for the risks for teratogenicity. It is noted that the risk exists across all trimesters of pregnancy.

Data from the report suggest some women with epilepsy, in addition to those with other conditions, continue to be prescribed valproate in pregnancy. In the March 2022 report, of the 247 female patients prescribed valproate in the month in which they were pregnant, 25 were identified as new additions to the registry in the most recent 6 months, April 2021 to September 2021. While there has been a reduction of 50% in the number of female patients prescribed valproate during pregnancy between April and September 2018 (the 6 months after the Pregnancy Prevention Programme was introduced) and April and September 2021, over the last 18 months numbers have plateaued (25 in April 2020 to September 2020, 21 in October 2020 to March 2021, 25 in April 2021 to September 2021). This raises concern that the initial impact of the risk minimisation measures has not been maintained or possibly even been reduced.

At the time of the March 2022 report of the registry, since April 2018, 23 female patients had received a prescription for valproate for the first time during pregnancy and had not been prescribed valproate in the previous 12 months. Three of these 23 female patients were new starters during April 2021 to September 2021. Of the 23 female patients, 8 were prescribed valproate only during the first trimester and stopped, 4 were prescribed during the first trimester and continued. The remainder were started after the first trimester or during the delivery month.

It is noted that CHM has been consulted on the effectiveness of the Pregnancy Prevention Programme on a number of occasions and has emphasised the importance of the registry in monitoring compliance.

The registry does not collate information on prescribing in male patients. Given there are currently no restrictions for male patients, prescribing is likely to be significantly higher than in female patients.

## 10.2 CPRD data for valproate prescribing in the UK

Data were assembled on valproate prescribing from the Clinical Practice Research Datalink and the British Health Foundation Trusted Research Environment to provide an overview of prescribing of valproate in different patient populations in the UK since 2010 and 2018 respectively.

Data showed that new use of valproate had been declining in adult male and female patients in all age groups particularly since 2014. The rate of decline was greatest in female patients aged 16 to 44 years, with the rate in 2021 about 10% of that seen in 2010, and there was a marked acceleration in the declining trend in 2017 to 2018.

The report showed that prescribing rates had plateaued in female patients with around 8 out of every 10,000 women aged 16-44 prescribed valproate in 2021. It also showed a much smaller decline has been seen in male patients of the same age and there was substantially higher initiation of valproate in male patients than was seen in female patients of the same age, around 28-30 in every 10,000 males aged 16-44 years.

Large declines in new prescribing in older patients were also seen in both male and female patients, with overall rates in those aged over 45 years in 2019 being 30% of those seen in 2010.

## 10.3 Further investigation of the potentially exposed pregnancies

In the [March 2022 report of the Medicines and Pregnancy Registry](#) 247 women in England were prescribed valproate in a month in which they were pregnant between the period April 2018 to September 2021.

In order to better understand the reasons for these pregnancies exposed to valproate, the MHRA and NHS Digital teams conducted a review, using hospital admissions data existing within the registry to further explore the potential indications for treatment and prescribing patterns.

The 247 women in this data set experienced a total of 259 potentially exposed pregnancies. Of the 247 women, 36 (14.6%) had a hospital admission for bipolar disorder or a similar psychiatric condition, as coded within the Hospital Episode

Statistics database, with no record of an admission for epilepsy. These 36 women experienced 42 pregnancies, 17 of which were estimated to have been conceived in April 2018 to March 2019, 9 in April 2019 to March 2020, 11 in April 2020 to March 2021, with the 5 remaining in the period April 2021 to Sept 2022. However, 11 out of the 36 also had a history of prescribing of another AED (including pregabalin and gabapentin).

181 (73.3%) women had a recorded hospital admission for epilepsy with no record of an admission for bipolar disorder or a similar psychiatric condition, while 7 (2.8%) women had a recorded hospital admission for both epilepsy and for bipolar disorder or a similar psychiatric condition.

Of the remaining 23 (9.3%) who had no record of admission for either bipolar disorder or epilepsy, 3 had a prescription for an antipsychotic but no prescription for an AED, 10 had a prescription for an AED but no prescription for an antipsychotic, 1 had a prescription for both, and 9 received only valproate.

Inferring of the indication for a prescription is challenging within electronic healthcare records, particularly when there are limited linkages to secondary care records as is currently the case within the registry. Furthermore, only prescribing data back to April 2018 were available, meaning it was not possible to explore more of a patient's prescribing history. However, these data suggest that while the majority of exposures during pregnancy are in patients with epilepsy, there continues to be pregnancies exposed to valproate outside of this patient population.

#### **10.4 Detailed follow up of the recent valproate-exposed pregnancies in the registry**

The MHRA conducted a review of the 25 pregnancies identified in the period April to September 2021 from the [March 2022 report of the Medicines and Pregnancy Registry](#) to understand better the histories of the women. This was done using the data available within the registry.

Of the 25 women pregnant on valproate, 20 were also dispensed an AED at some point since April 2018 and either dispensed no antipsychotic or had only been prescribed valproate and had a hospital admission for epilepsy and none for a relevant psychiatric condition, so it might be presumed that these 20 were prescribed valproate for epilepsy. Twelve of these 20 women were on valproate and at least one other AED just before estimated conception and continued

valproate in pregnancy. Of the 20 women, 7 were only receiving valproate, although one was also prescribed another AED in the month of conception for the first time, possibly suggesting switches in treatment. The final patient in this group had their last prescription for valproate 2 months prior to pregnancy and then were reissued with it only in the month prior to delivery.

Of the 25 women pregnant on valproate, 3 have also been dispensed an antipsychotic at some point since April 2018 and no other AED or have only been prescribed valproate but had a hospital admission for a relevant psychiatric condition but none for epilepsy, so it might be presumed that they were treated for bipolar disorder. One had their first prescription for valproate in the month of conception. The remaining 2 had prior use of valproate although one had their last prescription in the month of conception.

The last 2 of the 25 have a history of both other AED and antipsychotic use. One received valproate in the estimated month of conception but since then had only received an antipsychotic and another AED. The other had not had valproate or another AED prior to pregnancy and received their only prescription for either in the month of conception.

## **10.5 Summary of circumstances of pregnancies where detailed information is available**

An exercise was undertaken to seek more detailed information through contact with the prescribing GPs on the circumstances of the 25 pregnancies. Data within the registry are anonymised and individual patients' data are protected. As the MHRA does not have access to patient level identifiable data, details of the 25 GP practices were provided by NHS Digital and the MHRA contacted them to discuss the following questions:

1. Can you confirm if this patient was prescribed valproate while pregnant? If yes, was the pregnancy known at the time of the prescription?
2. What was the indication for the prescribing of valproate and what other medicines was this patient on at the time of pregnancy for this indication? How long had the patient been prescribed valproate?
3. Were any attempts made to switch the patient off valproate, or titrate to a lower dose, prior to pregnancy?



4. Prior to pregnancy, when had they last been seen by a specialist with regards to their valproate prescription?
5. Did they have a signed [valproate Annual Risk Acknowledgment Form](#)? How long before pregnancy was this completed?
6. Was the patient on contraception? What contraception? If not, why not?
7. Was any action taken when exposure in pregnancy was established?
8. Does the patient remain on valproate?

In order to identify their own patients within their records, GPs were able to contact NHS Digital directly to obtain patient NHS numbers. These data were not shared with MHRA.

Discussions were held with 9 of the 25 GP practices. In one case, the practice stated that the patient identified as taking valproate during pregnancy was not exposed during pregnancy.

Of the 8 women verified to have become pregnant while prescribed valproate, the majority of the pregnancies were in women taking valproate for epilepsy. In half of the cases where information was available the pregnancies were planned. In most of the cases there was evidence that the risks of valproate had been discussed, although ARAFs were documented in the patient's GP notes in only 3 cases.

No single issue or barrier to compliance with the Pregnancy Prevention Programme was raised, but issues given included the information exchange across care settings, waiting times for secondary care appointments and uncertainties around the transfer of responsibilities between healthcare professionals.

# 11. Patient and public evidence considered by CHM

Recent media reports have highlighted the cases of a number of women with valproate-affected pregnancies who state they were not informed of the risks associated with valproate. Equally, there are media reports advocating for informed choice for women where valproate is an effective medicine.

To inform their recommendations the CHM carefully considered data and views provided by patients, charities and other organisations as part of their review in 2022.

## 11.1 Valproate Stakeholder Network

The Valproate Stakeholder Network (VSN) brings together a range of stakeholders including patients, carers, patient representatives from a number of charities, clinicians and representation from healthcare partners. The VSN provides a “joined up” approach to sharing communications and raising awareness to optimise risk minimisation measures for the use of valproate.

The VSN includes representatives from 46 organisations including

- healthcare professional representative bodies
- charities that represent patients in relation to the two approved indications of epilepsy and bipolar disorder, plus migraine
- the leading patient support groups
- health system agencies (NHS, National Institute for Health and Care Excellence (NICE))
- Devolved Administrations (representing Scotland, Wales, and Northern Ireland)

Since its establishment in 2016, this group has inputted and advised on the impact of risk minimisation measures. More specifically they advised on the patient toolkit, feedback on the effectiveness of distribution of tool kit materials and feedback on the provision of valproate in white boxes without statutory information.

For the 2022 review, the VSN was asked to contribute their views on the current pregnancy prevention measures and how effective they had been (see below).

Following the review, the VSN also provided feedback on the patient-facing materials, which had been updated to reflect the CHM's recommendations, to ensure these were clear and addressed the needs of patients.

## **11.2 Evidence from experts, patient charities and other organisations**

### **11.2.1. Evidence sought from the patients and stakeholders**

In advance of the June 2022 CHM meeting, two sessions were held to allow CHM to hear directly from patients and other representatives with experience of sodium valproate. These sessions were held on 20 May and 10 June.

The focus of these sessions was to hear the views and experiences of sodium valproate and its prescribing following the additional risk measures introduced in 2018. Both sessions were online, providing members of the CHM with the opportunity to hear directly from patients and representatives prior to their meeting.

To aid the assessment of these important discussions, the CHM asked to hear directly from a wide range of people on the following questions:

1. Based on your experiences of Sodium Valproate, how well do you think the risks of valproate are explained in regulatory patient information materials?
2. Based on your experience of Sodium Valproate how effective do you feel the risk minimisation measures have been since they were introduced in 2018 and what future risk minimisation measures would you like to see associated with Sodium Valproate?

### **11.2.2. Views of patients and patient charities**

A patient support group dedicated to raising awareness of valproate risks in pregnancy felt that the current information to patients on valproate was appropriate and sufficient but that healthcare professionals were not doing enough to warn women of the harms associated with valproate. They spoke of

evidence that warnings were not given with the dispensed medication in 'white boxes' and that the right conversations were not happening with patients.

The patient support group gave evidence from a survey of members that said more than 25% of respondents were not warned of the dangers and only 5% were offered pre-conception counselling. A patient support group survey on pregnancy outcomes of their membership reported that, of people who completed the survey, 94% of their children who were exposed to valproate in pregnancy had been diagnosed with autism. The group said they were not calling for ban on valproate as some women need it but given the availability of alternative effective AEDs, new patients should not be prescribed valproate.

Evidence was then provided by a leader for a programme of work to support community nurses and midwives to identify opportunities to make a positive difference in pregnancy. They spoke about use of valproate outside of the main indication for epilepsy and that sometimes people do not feel the warnings are relevant to them because they are not using valproate for epilepsy. They noted that many pregnancies are unplanned, and that pre-conception care cannot be provided for these pregnancies. They noted that it can take months to find another medicine for epilepsy and that unplanned pregnancies do not allow time for this. They spoke of the need for accessible advice suitable for all patients, including the most vulnerable populations.

An epilepsy charity presented evidence based on their experience from patients ringing their helplines. They said most calls are from women who feel forced to take part in the valproate Pregnancy Prevention Programme when their chances of pregnancy are non-existent. They noted that these women felt they had no choice and were not listened to.

The charity noted that many doctors are reluctant to prescribe outside of the licence, for example in people with severe learning disabilities. They also noted confusion about the roles of the different types of healthcare professionals in relation to completion of the Annual Risk Acknowledgement Form. They noted that GPs need more support and education.

The charity felt that the [targeted letter](#) sent to all female patients on valproate by NHS England needs to happen on a regular basis, more than once a year, and that there should be regular communications with patients on the risks.

Long term, the charity felt there should be research to determine which pregnancies are vulnerable to valproate so that patients who are not at risk of harm can remain on treatment. They noted reports on social media of a patient who had switched from valproate and then died of a seizure.

A charity dedicated to supporting young people with epilepsy felt that conversations with patients about contraception can be difficult. They noted that having warnings on the labelling of medicines is good but not everyone is being reminded of the risks and not everyone is reviewed regularly. They felt that valproate does remain the best treatment for some patients, but these patients should be reviewed every year.

Another epilepsy charity welcomed the decrease in prescribing in female patients and increasing awareness of the harms of valproate in pregnancy, however they remained concerned that a small group of patients remained unaware and more needs to be done to ensure all patients are informed. They also noted that more should be done to research and communicate the risks with other AEDs.

The charity noted that they receive a lot of calls about the current restrictions on valproate and how they are implemented in terms of those for whom the Pregnancy Prevention Programme is problematic for reasons of religion, sexuality, or underlying conditions, for example learning disabilities. They spoke of patients who were distressed about constant conversations about the need for contraception.

The charity felt the patient materials need to reflect the needs of trans male patients who need to be on contraception. They also noted enquiries from men about fertility and transgenerational issues and said there was a need for robust evidence on these issues.

### **11.2.3. Views of healthcare professionals and their representatives**

A pharmacist presented a [study on changes in valproate prescribing and exposure across different populations](#). This study showed that the annual incident and prevalent rates of valproate prescribing declined for women aged between 14-45 years between 2011 and 2019. Statistically significant changes occurred around the time of MHRA safety alerts (published as McTaggart and others, 2022).

An organisation representing neurologists spoke of clinical issues in implementing the Pregnancy Prevention Programme. They felt that the ARAF should be digitally enabled to enable the form to be shared across different healthcare professionals and settings.

An association representing epilepsy nurses spoke of confusion caused by different information on contraception between the Patient Information Leaflet and the ARAF. They also noted the importance of having a digital ARAF. They felt there should be an audit of the number of women on valproate who do not want to change treatment.

A representative from a professional membership body of GPs spoke of the complexity of the wider healthcare system and that agreement of the roles of GPs and specialists within a shared care protocol is needed. It was further noted that an electronic ARAF should be developed to enable communication across the system.

A representative felt that the risk minimisation materials were not focused on minimising the risks but rather on the restrictions in use. They noted that women get upset and angry, especially because unlike other medicines, doctors cannot stop prescribing if a woman is not compliant with the pregnancy prevention measures. It was suggested there should be further exploration of the situations that led to a pregnancy being exposed to valproate and who made the decision on risk. The representative also noted alternative options for pregnancy.

#### **11.2.4. Conclusions**

The CHM listened closely to all of the evidence and asked questions when required to understand more about each perspective. The CHM considered the testimonies carefully when making their recommendations.

The CHM noted the vital contributions of patient support groups, charities, and healthcare professionals in providing very important information for the regulatory discussions on valproate. The CHM noted that the testimonies raised issues of compliance with the Pregnancy Prevention Programme and that it was clear that more needed to be done to protect patients.

The CHM noted the feedback from presentations about the complexity of implementation of the PPP and recommended better capture of the exposed population in secondary and tertiary care settings, an extension and digitisation of

the ARAF, and a consideration of where the clinical responsibility for the annual review of risk should lie.

The CHM advised that further efforts should be made to improve educational materials for both healthcare professionals and patients. It was suggested that educational materials communicating the risks of valproate needed to be tailored for relevant patient populations and should better reflect the needs of people with changing gender assignment or undergoing gender recognition.

## 12. Other data considered in the review

### 12.1 International Post-Market Surveillance (IPMS) Group Data

Information was sought by the MHRA from the International Post-Market Surveillance (IPMS) Group to understand how valproate is used in other countries.

The IPMS group consists of the following international regulatory agencies: Therapeutic Goods Administration (Australia), MedSafe (New Zealand), US Food and Drug Administration (USA), Health Canada, Health Sciences Authority (Singapore) and Swissmedic (Switzerland).

The answers to the following questions were sought from the IPMS group:

1. Has your agency undertaken or plans to undertake regulatory action to minimise the risk of valproate use in pregnancy? If so, can you please outline what measures have been taken.
2. Is the use of valproate in women of childbearing potential or age specifically monitored in your country? If so, could you provide the latest available usage data and highlight the impact your measures have had on prescribing levels.
3. Is your agency aware of cases of pregnancy in women prescribed valproate? If so, please provide details of the cases and confirm whether these cases being followed up?

Regulators from USA, Canada, Australia, New Zealand, Singapore, and Switzerland provided responses to these questions about valproate.

The US FDA's primary risk management tool for valproate is communication through the prescribing information (package insert). This includes a boxed warning about fetal risk. The other regulators have a similar regulatory position and Pregnancy Prevention Programme as in the UK. Where data on valproate usage were provided, there had been a reduction in the use of valproate in women of childbearing age. Apart from the North American Antiepileptic Drug (NAAED) Pregnancy Registry, the only data provided on exposed pregnancies was from spontaneous reporting databases.



## 13. Discussion and conclusions

While prescribing of valproate to women of childbearing potential has clearly reduced in recent years, data from the [March 2022 report of the Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England](#) show a further 25 women were recorded as newly pregnant and were prescribed valproate in the period between April 2021 to September 2021 in England. Of the 8 women verified to have been pregnant while prescribed valproate, 7 were taking valproate for epilepsy. In half of the cases (where information was available) the pregnancies were planned. In most of the cases there was evidence that the risks of valproate had been discussed, although ARAFs were documented in the patients GP notes in only 3 of the 8 cases.

Following a recent [comprehensive safety review in 2021 by the MHRA and CHM](#), it is advised that lamotrigine and levetiracetam are safer medicines for use during pregnancy since data suggests they are not associated with an increased risk of birth defects. Further efforts are required to ensure women of childbearing potential are switched to these safer medicines before pregnancy.

There are currently no specific risk minimisation measures for male patients other than the limited warnings in product information regarding infertility. Recent data from CPRD demonstrate continued prescribing and far higher prescribing in male patients than in females, with a suggestion of increased prescribing in recent years in young males aged 12 to 15 years of age. Given concerns about evolving data on the safety of valproate in males, proposals to further strengthen risk minimisation across all age groups and genders would reduce the risk that individuals may be treated with valproate when there may be other effective treatments with less serious risks.

The literature provides some evidence that valproate has HDAC inhibitory properties, which may provide a vehicle for epigenetic change. There is evidence from the literature that valproate has effects on multiple cellular signalling pathways, produces alterations in the expression of multiple genes and impairs mitochondrial function via several mechanisms.

The endocrine and hormonal effects of valproate are well known and there are extensive data demonstrating the testicular toxicity of valproate in sexually mature animals. Warnings on adverse effects on male fertility have been in the product information for some time.

Product information has been updated to reflect the totality of preclinical data showing testicular toxicity in adult rats and dogs and juvenile rats. Further clinical study on the effects of valproate on the endocrine and reproductive function of males is required to understand the clinical relevance of the preclinical studies.

Given the established harm in children born to mothers prescribed valproate during pregnancy, and signals of the potential for endocrine and reproductive effects in males, combined with unknown risks associated with paternal exposure and transgenerational effects, the totality of evidence for the harmful effects of valproate continues to build.

Given the recent evidence of limited impact of existing risk minimisation measures, continuing with efforts to raise awareness and enforcement of the current restrictions alone is felt unlikely to deliver significant additional progress in reducing the numbers of exposed pregnancies. It was also noted there had not previously been specific regulatory communications on the potential risk of infertility in males.

The implementation of more restrictive risk minimisation measures needs to balance the health of the unborn child with those of ensuring the mother has effective control of her epilepsy or bipolar disorder.

Therefore, in the context of the latest evidence for reduced effectiveness of the current risk minimisation measures in preventing new exposed pregnancies to valproate for both epilepsy and bipolar disorder; ongoing use of valproate in the UK in women of childbearing age; higher and potentially increasing usage in males, in particular in young males; off label use of valproate in other indications; the signal from preclinical data of testicular toxicity in juvenile animals combined with known fertility problems in adult males following valproate exposure; and clear evidence that switching to other treatment options where benefit-risk would be more favourable has been achieved in women of childbearing potential, consideration of further more stringent risk minimisation measures is warranted.

## **14. CHM advice sought on the assessment**

On the basis of the evidence provided, the CHM was asked to advise on whether the risk–benefit profile of valproate has changed in any population or for any indication and whether the current risk minimisation measures were effective and sufficient. If not, the CHM was asked to advise on which of a range of additional risk minimisation options were proportionate and whether these should apply to all indications, genders and/or age ranges.

A range of regulatory options were presented to the CHM by the MHRA for their advice.

The CHM considered how to balance further regulatory actions to protect patients with potential unintended consequences, including increasing rates of uncontrolled epilepsy and mental health relapse or suicide.

## 15. CHM advice on the review

On the basis of the evidence presented of continued exposure to valproate in pregnancy despite the Pregnancy Prevention Programme; the concerning evidence of testicular toxicity in juvenile and adult animal studies with potential impact for human males, known risk of male infertility and uncertain risk transmission via paternal exposure; the potential epigenetic effects of valproate and potential for transgenerational risk transmission of harm; and taking into account the views of the patients and other stakeholders, the CHM advised that minimisation of the risk of harm from valproate requires further regulatory action, and a strengthened system response.

The CHM expressed significant concern about the evolving data in the literature on the potential epigenetic effects of valproate. Given the evidence in the literature for the histone deacetylase (HDAC) inhibitory properties of valproate, the CHM advised that information about HDAC inhibition should be included in the Summary of Product Characteristics and this is being considered separately by the Valproate Epigenetics Expert Working Group.

The CHM noted the results of the published French support-charity family survey, which reported that of 108 individuals (from 90 families) who had adverse effects from valproate exposure in-utero who were parents themselves (85 women and 23 men), 23% of their children were born with malformations and 44% were born with neurodevelopmental disorders (Martin and others, 2022). The CHM noted limitations in interpreting the data from the survey but agreed this clinical evidence was important. The CHM also noted the progress of the studies by the Marketing Authorisation Holders in evaluating the impact of valproate on the epigenome of the male and female germ cell in animals. The CHM advised more urgency was required in progressing studies into the transgenerational risk and advised exploring both academic research collaborations and how CPRD might help with family identification to strengthen the clinical data set.

The CHM recommended a number of regulatory actions to further strengthen safety measures for valproate including further warnings in the product information, strengthened educational materials and enhanced monitoring of the use of valproate across all ages, populations and indications to address the concerns. The CHM recommended that the MHRA should work closely with health system bodies to support effective implementation of the new regulatory measures.

A summary of the advice of the CHM is detailed below.

The CHM advised that:

- a. the balance of risks and benefits of valproate in those under 55 was unfavourable unless there is no other effective or tolerated treatment

- b. no new patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment
- c. the SmPC should be updated to reflect the available information on HDAC inhibition
- d. an updated risk acknowledgement form to reflect the risks in all populations under 55 years is required and that digitalisation is a priority with improved system support in secondary care for identifying patients for review
- e. updated patient materials are required to support revised information in the SmPC on the risk to male patients under the age of 55 years and the potential for transgenerational effects and to better reflect the needs of patients with gender reassignment. Information about teratogenic and transgenerational risks in males over 55 years planning a family should also be reflected
- f. The RMP should include a requirement for a mandatory drug registry for all patients under 55 years of age

The Commission recommended:

- a. existing drug management systems should be explored for managing valproate prescribing such as systems for managing high-cost medicines whereby doctors complete a form for any patient who is prescribed a high cost drug.
- b. further research is urgently needed to evaluate the epigenetic risks of valproate and the impact on patients and subsequent generations

## 16. Advice of the CHM Valproate Implementation Expert Working Group

The CHM recognised that successful implementation of the new measures would require a significant change in clinical practice and established the Valproate Implementation Expert Working Group (VIEWG) to advise on their safe and effective introduction. The VIEWG included representatives from professional bodies and healthcare system bodies including NHS England (NHSE), the Care Quality Commission, the General Medical Council, the General Pharmaceutical Council, NICE, and the Devolved Administrations representing Scotland, Wales, and Northern Ireland.

The terms of reference of the VIEWG were to inform the CHM on:

- pathways and strategies for implementing the recommendations of the Commission on Human Medicine on valproate,
- communication and educational materials to support and record informed prescribing decisions,
- plans for measurement of compliance with the new regulatory requirements,
- plans for determining the impact of the updated regulatory position and associated communications.

The VIEWG met 11 times between October 2022 and September 2023 and reported back to the CHM several times on clinical considerations to support safe implementation of the new measures. A summary of the main advice of the VIEWG on the first 2 aspects of their terms of reference is as follows:

- Implementation of the new regulatory position should be phased.
- Stakeholders should be made aware of the totality of the evidence including latest clinical data and in light of this data, the views of stakeholders should be sought on implementation plans.
- The two-signature approach should be configured to minimise any prescribing delays.
- Multi-Disciplinary Teams could be used to support two specialist decision-making.
- Clinical guidance is needed to interpret the new regulatory position and should be updated.
- Balanced decision-making tools should be developed with stakeholders.

- Implementation should be adequately resourced, including a digital Annual Risk Acknowledgement Form.
- Valproate-exposed pregnancies should be evaluated in a multidisciplinary framework, with learnings fed back to improve care.
- Further consideration should be given to flexibility of the two-specialist system, especially to address stakeholder concerns about impacts on autonomy.

Systems should be in place as soon as possible to measure the outcome of the review. The detailed advice of the VIEWG is at Annex 1.

As of November 2023, the VIEWG are still to meet to advise on options for measuring the compliance with, and impact of the introduction of the new measures.

## 17. Stakeholder feedback

The MHRA held stakeholder engagement sessions on 12 December 2022 prior to announcement of the advice of the CHM on the MHRA's website and in [December 2022 Drug Safety Update](#). A meeting of the Valproate Stakeholder Network (VSN) was held on 12 January to enable the insights from a range of stakeholders to inform discussions at the VIEWG.

Key issues raised at the VSN meeting on 12 January 2022 are summarised below:

- Feedback on the measures – concerns were raised about the proportionality and safety of the two specialist requirement and the possible negative impact of the measures on the health system and individuals.
- The need for clear and consistent messaging, guidance and support for healthcare professionals and patients.
- The need to monitor the effectiveness and unintended consequences of the measures.
- The need for shared decision making in prescribing decisions ensuring the inclusion of patient views.
- The need for wider stakeholder input at the VIEWG.

Some charities and groups formed a coalition to present their joint concerns and MHRA met with the coalition on 21 June 2023 to further discuss the issues raised.

Members of the Valproate Stakeholder Network provided extensive input to the draft male risk form and updated Patient Guide. Their suggestions were carefully considered and where possible, resulted in changes to these materials.



## **18. CHM consideration of the VIEWG and stakeholder views and updated CHM advice**

The CHM carefully considered the advice of the VIEWG and the views of stakeholders on a number of occasions in 2023. In addition, the CHM has kept abreast of the evolving data from the study on outcomes in children whose fathers took valproate. The revised study analysis will be carefully re-assessed by the MHRA and any further guidance will be communicated to patients and healthcare professionals as soon as possible.

The CHM discussed the feedback from the VIEWG that an anticipated influx of male patients to be reviewed by two specialists may divert consultant resource away from other areas of neurology service, including review of women of childbearing potential, a group in which the reproductive risks are a magnitude greater than those estimated for male patients. The CHM agreed to a phased approach to implementation, and flexibilities on the method for obtaining the second specialist review, including the use of multidisciplinary teams and remote consultation with the second signatory.

The CHM discussed the known risk factors for Sudden Unexplained Death in Epilepsy (SUDEP) including poorly controlled seizure disorders.

The CHM discussed the findings of the Standard and New Antiepileptic Drug (SANAD I and II) studies (Marson and others, 2007; Marson and others, 2021). The CHM considered that while the efficacy advantage of valproate over other antiseizure medications in generalised epilepsies was demonstrated, these studies do not take into account risks, in particular the established and emerging serious reproductive harms of valproate.

For focal epilepsy, SANAD showed that lamotrigine should remain a first-line treatment for patients.

The CHM discussed that patient autonomy in decision making about their treatment should be supported in all communications. In addition, there was also a need to consider advice for those patients prescribed valproate off-label for intellectual disability, brain injury or in forensic psychiatry; some of whom may lack capacity and may not be within the standard care pathways being targeted with communications.

The CHM discussed the ethical dilemma of patients who might be sexually active refusing contraception and that while autonomy in decision making is supported, the risks to the unborn child are important to decision making.

The CHM discussed the importance of consistent messaging for patients and that wherever possible the communications from MHRA, patient charities and healthcare professional organisations should be consistent.

The CHM considered the definitions of the term “specialist” proposed by the VIEWG in reference to the valproate product information, and to be adopted in clinical guidelines and MHRA communications. The Commission suggested some amendments to ensure the specialists described represented an appropriate level of increased clinical oversight of valproate prescribing.

The CHM advised that the second specialist signatory could include the following:

- Consultant adult or paediatric neurologists
- Consultant psychiatrists
- Speciality and associate specialist doctors in psychiatry and neurology
- Speciality doctors in psychiatry
- Paediatrician with special interest in epilepsy
- Paediatrician who regularly manages complex epilepsy or bipolar disorder
- Epilepsy Nurse Consultant
- Specialist Nurses in relevant disciplines

The CHM also advised on the level of independence required of the second specialist. CHM advised that the second signatory for initiation of valproate treatment and the decision to continue or switch valproate treatment should not be in direct line management of the primary signatory. Multidisciplinary Teams (MDTs) could be used to discuss and agree a prescribing decision, with the second signatory being a representative of the MDT who meets the criteria for a specialist signatory. The details of the two signatories should be recorded in the Risk Acknowledgement Forms for female and male patients.

In June 2023, on the basis of the totality of the evidence for harm and the availability of other treatment options for many patients where the benefit-risk would be more favourable, the CHM confirmed their previous advice that no new patients under the age of 55 years should be started on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment and advised that:

- a. the initial phase of implementation of the new regulatory position will apply to all patients under 55 years newly starting valproate and the prevalent female population (girls and women of childbearing potential).
- b. for girls and women already taking valproate the two-specialist system should be implemented at their next routine review.
- c. for men currently taking valproate the requirement for the two-specialist review will begin in the subsequent phase of implementation, which will take into account advice from healthcare professionals and patients developed in light of experience with the initial phase.

The CHM again supported engagement with relevant stakeholders on the valproate risk minimisation materials to ensure these are clear and understood by patients and noted that implementation will be supported by communications to key organisations ahead of announcement. The Valproate Implementation Expert Working Group noted the National Patient Safety Alert to help ensure system readiness.

## **18.1 Post-authorisation Safety Study on Paternal Transmission of Risk with Valproate**

Earlier this year, MHRA received the results of a study, which had been commissioned by the European Medicines Agency, on outcomes in children whose fathers took valproate in the 3 months before conception. A [high-level description of the study](#) is publicly available on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) website.

While some regulators announced regulatory changes on the basis of the results communicated early in 2023, errors were subsequently identified in the original data which required re-analysis. The revised study analysis will be carefully re-assessed by the MHRA and any further guidance will be communicated to patients and healthcare professionals as soon as possible.

## 19. Updated risk minimisation materials

When the valproate Pregnancy Prevention Programme was implemented in 2018, risk minimisation materials were made available (digitally and in hard copy) to healthcare professionals and patients to supplement the information given in the statutory patient information leaflet and to support informed decision making. These included a patient card, patient booklet, healthcare professional booklet, pharmacy poster and Annual Risk Acknowledgement Form. These materials are produced and disseminated by the marketing authorisation holders and approved by the MHRA.

To support the implementation of the new measures for valproate, the existing risk minimisation materials for the PPP are being updated and a new Risk Acknowledgement Form for male patients starting valproate is being developed. The Valproate Stakeholder Network provided important input to this form, as well as the updated Patient Guide. The risk minimisation materials and their purpose are summarised below.

<b>Educational material</b>	<b>Purpose</b>
<b>Updated Healthcare Professional Guide</b>	Provides up to date information for healthcare professionals on risks of valproate in pregnancy and the risks for male patients, the new conditions of valproate prescribing and key points for patient discussions.
<b>Updated Patient guide</b>	Provides those taking valproate (or their parent/caregiver/responsible person) with up to date information on risks of valproate in pregnancy and the risks to male patients and what they need to do.
<b>Updated Annual Risk Acknowledgement Form</b> for female patients starting valproate and at annual review	Used to support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist.
<b>New Risk Acknowledgement Form</b> for male patients starting valproate	Used to support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males starting treatment with valproate and to record the decision of the countersigning specialist.
<b>Patient card</b>	Provides key information for female patients receiving valproate on contraception and pregnancy prevention.
<b>Pharmacy poster</b>	Provides important actions for pharmacists dispensing valproate to female patients.
<b>Warning stickers</b>	To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

The updated risk minimisation materials will be available digitally on the [MHRA website](#) and the [electronic medicines compendium](#). Links will also be available via a QR code provided in the Patient Information Leaflet. Hard copies of the materials will be sent to healthcare professionals within 6-8 weeks of the change to the marketing authorisations. On receipt of the new materials, healthcare professionals should discard previous versions.

## 20. Next steps

The MHRA has issued a National Patient Safety Alert, with agreement from healthcare bodies, to ask providers of care to take necessary actions to enable implementation of the new safety measures. See our public statement for more information.

Further communications will follow on the introduction of safety measures after the regulatory changes are made and new educational materials are available.

Full adherence to the Valproate Pregnancy Prevention Programme must continue during implementation of these new measures. Any patient who thinks they are pregnant while on valproate should be advised to talk to a specialist urgently.

The MHRA will monitor the impact of the new measures and seek advice from the CHM and other invited experts as needed. Feedback from the implementation of the initial phase in new starters and the prevalent female population will inform the implementation of the measures for male patients under the age of 55 already taking valproate.

The revised study analysis will be carefully re-assessed by the MHRA and any further guidance will be communicated to patients and healthcare professionals as soon as possible.

Further studies will be initiated on the risks of valproate. The MHRA will monitor the findings of these studies closely and take action promptly.

If you are a patient on valproate please discuss any concerns you have with your healthcare professional. No-one should stop valproate without advice from their healthcare professional. A healthcare professional will advise on other suitable treatments and how to switch medication safely.

## 21. References

European Medicines Agency/Pharmacovigilance Risk Assessment Committee (PRAC). [Substances related to valproate \(EMA/686022/2014\)](#). Published on 9 October 2014.

L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). [Caisse nationale de l'Assurance Maladie \(CNAMTS\) study - part I. 2017](#).

Alsouk BA. [Neurodevelopmental outcomes in children exposed prenatally to levetiracetam](#). Therapeutic Advances in Drug Safety 2022: volume 13.

Bairy L and others. [Reproductive toxicity of sodium valproate in male rats](#). Indian Journal of Pharmacology 2010: volume 42, pages 90 to 94.

Ban L and others. [Congenital anomalies in children of mothers taking antiepileptic drugs with and without periconceptional high dose folic acid use: a population-based cohort study](#). PLOS ONE 2015: volume 10.

Bech BH and others. [Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study](#). British Medical Journal 2014: volume 349, pages 1 to 11.

Bromley RL and others. [Early cognitive development in children born to women with epilepsy: a prospective report](#). Epilepsia 2010; 51: 2058–65.

Bromley RL and others. [The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs](#). Journal of Neurology, Neurosurgery and Psychiatry 2013: volume 84, pages 637 to 643.

Bromley R and others. [Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child](#). Cochrane Database Syst Rev 2014, Issue 10.

Cansu A and others. [Effects of chronic treatment with valproate and oxcarbazepine on testicular development in rats](#). Seizure 2011: volume 20, pages 203 to 207.

Chen H, Dzitoyeva S, Manev H. Effect of valproic acid on mitochondrial epigenetics. Eur J Pharmacol. 2012 Sep 5;690(1-3):51-9. doi: 10.1016/j.ejphar.2012.06.019. Epub 2012 Jun 20. PMID: 22728245; PMCID: PMC3419440.

Choi CS and others. [The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy](#). Scientific Reports 2016: volume 6, pages 1 to 11.

Christensen J and others. [Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring.](#) JAMA Network Open 2019: volume 2, article e186606.

Christensen J and others. [Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism.](#) JAMA 2013: volume 309, pages 1696 to 1703.

Clayton-Smith J and others. [Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability.](#) Orphanet Journal of Rare Diseases 2019: volume 14, pages 1 to 21.

Cohn D and others. [The effect of anticonvulsant drugs on the development of male rats and their fertility.](#) Journal of Neurology, Neurosurgery, and Psychiatry 1982: volume 45, pages 844 to 846.

Cohen MJ and others. [Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years.](#) Epilepsy Behav 2013; 29: 308–15

Conei D and others. [Protective role of vitamin E in testicular development of mice exposed to valproic acid.](#) First International Journal of Andrology Andrologia 2021: volume 53, article e14140. <sup>a</sup>

Conei D and others. [Valproic acid during pregnancy decrease the number of spermatogenic cells and testicular volume in the offspring of mice: Stereological quantification.](#) Histology and Histopathology 2021; volume 36, pages 1189 to 1198. <sup>b</sup>

Coste J and others. [Risk of early neurodevelopmental disorders associated with in utero exposure to valproate and other antiepileptic drugs: a nationwide cohort study in France.](#) Scientific Reports 2020: volume 10, pages 1 to 11.

Cummings C and others. [Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine.](#) Arch Dis Child 2011; 96: 643–47.

Davis R and others. [Valproic acid: a reappraisal of its pharmacological properties and clinical efficacy in epilepsy.](#) Drugs 1994: volume 47, pages 332 to 372.

Engeland A and others. [Effects of preconceptional paternal drug exposure on birth outcomes': cohort study of 340000 pregnancies using Norwegian population-based databases.](#) British Journal of Clinical Pharmacology 2013: volume 75, pages 1134 to 1141.

European Medicines Agency/Pharmacovigilance Risk Assessment Committee (PRAC). [Substances related to valproate \(EMA/686022/2014\).](#) Published on 9 October 2014.

European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC). [Medicinal products containing substances related to valproate \(EMA/198940/2018\).](#) Published on 8 February 2018.

Faculty of Sexual & Reproductive Healthcare. [FSRH Clinical Guideline: Contraception for Women Aged over 40 Years \(August 2017, amended July 2023\)](#).

Finnell RH and others. [Gene Environment Interactions in the Etiology of Neural Tube Defects](#). Frontiers in Genetics 2021: volume 12.

Fromenty B, Pessayre D. [Impaired mitochondrial function in microvesicular steatosis. Effects of drugs, ethanol, hormones and cytokines](#). Journal of Hepatology 1997: volume 26, pages 43 to 53.

Gesche J and others. [Resistance to valproic acid as predictor of treatment resistance in genetic generalized epilepsies](#). Epilepsia 2017: volume 58, pages e64 to e69.

Houtepen LC and others. [DNA methylation signatures of mood stabilizers and antipsychotics in bipolar disorder](#). Epigenomics 2016: volume 8, pages 197 to 208.

Iamsaard S and others. [Valproic acid induces histologic changes and decreases androgen receptor levels of testis and epididymis in rats](#). International Journal of Reproductive Biomedicine 2017: volume 15, pages 217 to 224.

Ibi D and others. [Paternal valproic acid exposure in mice triggers behavioral alterations in offspring](#). Neurotoxicology and Teratology 2019: volume 76, article 106837.

Jia H and others. [HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation](#). Proceedings of the National Academy of Sciences of the United States of America 2014: volume 112, pages E56 to E64.

Jentink J and others. [Does folic acid use decrease the risk for spina bifida after in utero exposure to valproic acid?](#) Pharmacoepidemiology and Drug Safety 2010: volume 19, pages 803 to 807.

Källén B. [Valproic acid is known to cause hypospadias in man but does not reduce anogenital distance or causes hypospadias in rats](#). Basic & Clinical Pharmacology & Toxicology 2008: volume 94, pages 51 to 54.

Khan S and others. [Investigation on sodium valproate induced germ cell damage, oxidative stress and genotoxicity in male Swiss mice](#). Reproductive Toxicology 2011: volume 32, pages 385 to 394.

Krogenaes AK and others. [Valproate affects reproductive endocrine function, testis diameter and some semen variables in non-epileptic adolescent goat bucks](#). Theriogenology 2008: volume 70, pages 15 to 26.

Kubota T and others. [Epigenetic understanding of gene-environment interactions in psychiatric disorders: a new concept of clinical genetics](#). Clinical Epigenetics 2012: volume 4, pages 1 to 8.



L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). [Caisse nationale de l'Assurance Maladie \(CNAMTS\) study - part I. 2017.](#)

Labbe G and others. [Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies.](#) Fundamental and Clinical Pharmacology 2008: volume 22, pages 335 to 353.

Leiknes KA and others. [Electroconvulsive therapy during pregnancy: a systematic review of case studies.](#) Archive of Women's Mental Health 2015: volume 18, pages 1 to 39.

Marson A and others. [The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial.](#) The Lancet 2007, volume 369, pages 1016 to 1026.

Marson A and others. [The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial.](#) The Lancet 2021, volume 397, 1363 to 1374.

Martin M and others. [Transgenerational adverse effects of valproate? A patient report from 90 affected families.](#) Birth Defects Research 2022: volume 114, pages 13 to 16.

Meador K and others. [Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts.](#) Epilepsy Research 2008: volume 81, pages 1 to 13.

Meador KJ and others. [Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs.](#) NEJM 2009; 360: 1597–605.

Meador K and others. [Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years \(NEAD study\): a prospective observational study.](#) Lancet Neurol 2013; 12: 244–52.

Mello MLS. Sodium Valproate-Induced Chromatin Remodeling. Front Cell Dev Biol. 2021 Apr 20;9:645518. doi: 10.3389/fcell.2021.645518. PMID: 33959607; PMCID: PMC8093769.

National Organisation for Rare Disorders (NORD). [Fetal Valproate Syndrome.](#) Published 1994. Last updated May 2020.

Nishimura and others. [Effects of valproic acid on fertility and reproductive organs in male rats.](#) The Journal of Toxicological Sciences 2000: volume 25, pages 85 to 93.

Orphaned. [Fetal valproate spectrum disorder.](#) Last updated April 2020.

Ourique GM and others. [Resveratrol prevents oxidative damage and loss of sperm motility induced by long-term treatment with valproic acid in Wistar rats.](#) Experimental and Toxicologic Pathology 2016: volume 68, pages 435 to 443.

- Paton C and others. [Who is prescribed valproate and how carefully is this treatment reviewed in UK mental health services? Data from a clinical audit.](#) Therapeutic Advances in Psychopharmacology 2022; volume 12. article 20451253221110016.
- Phiel CJ and others. [Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen.](#) Journal of Biological Chemistry 2001: volume 276, pages 36734 to 36741.
- Rosenberg G. [The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?](#) Cellular and Molecular Life Sciences 2007: volume 64, pages 2090 to 2103.
- Royal College of Psychiatrists. Guidance. [Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness](#) 2018.
- Semczuk-Sikora A and others. [Valproic acid transfer across human placental cotyledon during dual perfusion in vitro.](#) Annals of Agricultural and Environmental Medicine 2010: volume 17, pages 153 to 157.
- Silva MFB and others. [Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: a review.](#) Journal of Inherited Metabolic Disease 2008: volume 31, pages 205 to 216.
- Snyder PJ and others. [Chronic administration of sodium valproic acid slows pubertal maturation in inbred DBA/2J mice: skeletal, histological, and endocrinological evidence.](#) Epilepsy Research 1995: volume 20, pages 203 to 211.
- Soliman GA and others. [Effects of antiepileptic drugs carbamazepine and sodium valproate on fertility of male rats.](#) DTW. Deutsche tierärztliche Wochenschrift 1999: volume 106, pages 110 to 113.
- Sveberg Røste L and others. [Effects of chronic valproate treatment on reproductive endocrine hormones in female and male Wistar rats.](#) Reproductive Toxicology 2002; Volume 16, pages 767 to 773.
- Sveberg Røste L and others. [Morphological changes in the testis after long-term valproate treatment in male Wistar rats.](#) Seizure 2001: Volume 10, pages 559 to 565.
- Tanabe and others. [Adverse Outcome Pathway on histone deacetylase inhibition leading to testicular atrophy.](#) OECD Series on Adverse Outcome Pathways. OECD Publishing, Paris 2021 number 17.
- Tallon E and others. [Reversible male infertility with valproate use: A review of the literature.](#) Epilepsy & Behavior Reports 2021: volume 16: article 100446.
- Tartaglione M and others. [Early Behavioral Alterations and Increased Expression of Endogenous Retroviruses Are Inherited Across Generations in Mice Prenatally Exposed to Valproic Acid.](#) Molecular Neurobiology 2019: volume 56, pages 3736 to 3750.

Thomas SV and others. [Motor and mental development of infants exposed to antiepileptic drugs in utero.](#) Epilepsy Behav 2008: pages 229 to 36.

Toledo M and others. [Expert opinion: use of valproate in girls and women of childbearing potential with epilepsy: recommendations and alternatives based on a review of the literature and clinical experience—a European perspective.](#) Journal of Neurology 2020: volume 268, pages 2735 to 2748.

Tomson T and others. [Valproate in the treatment of epilepsy in girls and women of childbearing potential.](#) Epilepsia 2015: volume 56, pages 1006 to 1019.

Tomson T and others. [Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry.](#) The Lancet Neurology 2018: volume 17, pages 530 to 538.

Vanya M and others. [Effects of maternal epilepsy and antiepileptic therapy in women during pregnancy.](#) Ideggyogy Sz 2015: volume 68, pages 105 to 112.

Veiby G and others. [Exposure to antiepileptic drugs in utero and child development: a prospective population-based study.](#) Epilepsia 2013: volume 54, pages 1462 to 1472.

Veroniki AA and others. [Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes.](#) BMC Medicine 2017: volume 15, pages 1 to 20.

Vijay P and others. [The effect of sodium valproate on the biochemical parameters of reproductive function in male albino Wistar rats.](#) Indian Journal of Pharmacology 2008; volume 40, pages 248 to 250.

Walker RM and others. [Preclinical toxicology of the anticonvulsant calcium valproate.](#) Toxicology 1990: volume 63, pages 137 to 155.

Weston J and others. [Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child.](#) Cochrane Database of Systematic Reviews 2016; issue 11, article CD010224.

## 22. Glossary of terms

### **Antiepileptic drug or AED**

A drug used to treat epilepsy, mainly by controlling or managing the occurrence of seizures in a patient with epilepsy. Also called anti-seizure medicine or epilepsy medicine.

### **Anti-seizure medication or ASM**

A drug used to treat epilepsy, mainly by controlling or managing the occurrence of seizures in a patient with epilepsy. This term may be more commonly used in UK clinical practice than antiepileptic drug.

### **Autism spectrum disorder**

Autism is a lifelong developmental disability which affects how people communicate and interact with the world. Autism is a spectrum condition and affects people in different ways.

### **Bipolar disorder**

Bipolar disorder is a mental health condition that affects moods and can make them swing from one extreme to another. It used to be known as manic depression. People with bipolar disorder have episodes of depression (feeling very low and lethargic) and mania (feeling very high and overactive). Unlike simple mood swings, each extreme episode of bipolar disorder can last for several weeks (or even longer).

### **Cleft lip or palate**

A cleft is a gap or split in the upper lip or roof of the mouth (palate). Cleft lip and palate can each occur alone or together. It is the most common facial birth defect in the UK affecting around 1 in every 700 babies.

### **Clinical data or clinical studies**

Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

### **Cohort study**

In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

### **Commission on Human Medicines**

The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

### **Confidence interval**

A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

**Confounds/confounding/confounded**

Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

**Congenital**

A medical condition that is acquired by the fetus during pregnancy and is present at birth.

**Congenital Malformations**

A physical defect present in a baby at birth that can involve many different parts of the body, including the brain, heart, lungs, liver, bones, and intestinal tract.

**Contra-indicated/Contraindication**

When a drug should not be used in a specific situation, condition or group of people because it may be harmful to the person.

**Defect**

A fault or imperfection in the body.

**Developmental Delay**

Where a child had not gained the developmental skills expected of them, compared to others of the same age. Delays may occur in the areas of motor function, speech language, cognition, play and social skills.

**Epidemiological studies**

Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

**Epigenetic / Epigenetic factors**

Epigenetics are how your behaviours and environment can cause changes that affect the way your genes work (your genetics)

**Epilepsy**

A brain condition characterised by fits or seizures.

**Generalised seizures**

A generalised seizure starts when all areas of the brain are affected by an abnormal electrical impulse and happen without warning. There are different types of generalised seizures, including: absence seizures (petit mal seizures), myoclonic seizures, and clonic seizures. The person will be unconscious (except in myoclonic seizures), even if just for a few seconds and afterwards will not remember what happened during the seizure.

**Good Laboratory Practice**

A set of rules and criteria intended to assure the quality and integrity of non-clinical laboratory studies.

**Healthcare databases**

Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient's care.

**Incidence**

The occurrence of new cases of a disease or condition in a population over a specified time period.

**Indication**

The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

**In-utero**

The time that the fetus is in the uterus of the pregnant female.

**Major congenital malformations**

Physical defects present in a baby at birth that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention.

**Marketing authorisation holder**

The company or other legal entity that has the authorisation to market a medicine in the UK.

**Meta-analysis**

A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

**Monotherapy**

The treatment of a disease or condition with a single medicine.

**Motor skills**

Motor skills are movements and actions of the muscles to perform a specific task. Fine motor skills refer to small movements in the hands, wrists, fingers, feet, toes, lips and tongue. Gross motor skills involve motor development of muscles that enable babies to hold up their heads, sit and crawl, and eventually walk, run, jump and skip.

**Myoclonic seizures**

Myoclonic means 'muscle jerk'. Myoclonic seizures are brief but can happen in clusters (many happening close together in time), and often happen shortly after waking. They are classified as generalised seizures because the person is likely to have other seizures as well as myoclonic seizures.

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

**Neonate**

Newborn infant.

**Neural**

Relating to a nerve or the nervous system.

### **Neural tube defects**

Neural tube defects are birth defects of the brain, spine, or spinal cord. The neural tube is the structure that eventually develops into the baby's brain and spinal cord. The neural tube starts to form in early pregnancy and closes about 4 weeks after conception. Spina bifida is a type of neural tube defect. In spina bifida, part of the neural tube does not develop or close properly, leading to defects in the spinal cord and bones of the spine (vertebrae).

### **Neurodevelopment**

A general term used to encompass the development of the nervous system.

### **Neurodevelopmental disorders and delay**

A group of disorders in which the development of the central nervous system is disturbed. The disorders can affect emotion, learning ability, self-control and memory. They can also manifest as conditions such as attention deficit hyperactivity disorder or autism spectrum disorder.

### **Neurogenic**

Effects or conditions giving rise to or arising from the nerves or the nervous system.

### **Neurons**

Nerve cells that send information to each other by releasing chemicals, known as neurotransmitters, across junctions known as synapses.

### **Non-clinical studies**

In drug development, preclinical development, also named preclinical studies and non-clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected. Used interchangeably with the term 'pre-clinical studies' within this report.

### **Patient Information Leaflet**

Every medicine pack includes a patient information leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

### **Partial seizures**

See focal seizures.

### **Pervasive developmental disorders**

A group of disorders characterized by delays in the development of socialization and communication skills. Parents may note symptoms as early as infancy, although the typical age of onset is before 3 years of age.

### **Pregnancy Prevention Programme**

A Pregnancy Prevention Programme is a set of measures that are intended to minimise the risk for the both the women and the unborn baby associated with the use of a medicine in women of childbearing age and during pregnancy.

**Pregnancy Registry**

A study that collects health information from women who take prescription medicines or vaccines when they are pregnant. Information is also collected on the newborn baby.

**Prenatal**

Before birth, during or relating to pregnancy.

**Prospective cohort study**

A prospective study asks a specific study question (usually about how a particular exposure affects an outcome), recruits appropriate participants, and looks at the exposures and outcomes of interest in these people over the following months or years.

**Retrospective study**

A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

**Risk factor**

A substance or activity that increases the likelihood of someone developing an illness or medical condition.

**Risk Ratio/Relative Risk**

A risk ratio (RR), also called relative risk, compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group.

**Seizure**

Uncontrolled electrical activity in the brain that produces fits or convulsions of the body.

**Spontaneous abortion**

Is the loss of a pregnancy naturally before 20 weeks of gestation.

**Summary of Product Characteristics (SmPC)**

Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at:

<https://www.gov.uk/guidance/find-product-information-about-medicines>

**Systematic review**

A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

**Teratogen/ teratogenic**

A teratogen is an agent that can disrupt the anatomical development of the embryo resulting in a birth defect.

**Tonic clonic seizures**

The type of epileptic seizure most people recognise. There are two phases to these seizures. In the first phase the 'tonic' phase the person will lose consciousness and won't be aware of what is happening, their muscles will go stiff and so they may fall (if standing) and



also bite their tongue. In the second phase the 'clonic' phase their limbs will jerk quickly and rhythmically and they may lose control of their bladder and/or bowels. They are likely to feel confused or sleepy afterwards and take a while to recover fully.

### **Transgenerational effects**

Transgenerational effects are effects that can pass from a mother or father through successive generations of a family, such as to children or grandchildren.

### **Trimester**

One of the three 3-month periods that a human 9-month pregnancy can be divided into.

# Annex 1

## Extract from Valproate Implementation Expert Working Group Chair's Summary of advice to CHM

### Introduction

Valproate is an effective drug for treatment of epilepsy and bipolar disorder, but concerns continue to grow about the extent of reproductive toxicities associated with its use. Following a comprehensive review the Commission on Human Medicines has advised a strengthened regulatory position. The Valproate Implementation Expert Working Group has been asked to provide advice on how the new regulations can be implemented as safely as possible within healthcare systems.

The terms of references are to advise the Commission on Human Medicines on:

- Plans for implementation in healthcare systems of the new advice of the Commission on Human Medicine on valproate
- Communication and educational materials to support and record informed prescribing decisions
- Plans for measurement of compliance with the new regulatory requirements and determining the impact of the risk minimisation measures

The implementation group heard a number of regulatory concerns, summarised as follows:

- The number of valproate-exposed pregnancies in the UK has stopped decreasing
- Emerging preclinical and clinical concerns about transgenerational risks of valproate
- Established and emerging concerns about reproductive harms in males. This includes preclinical reproductive toxicity, clinical concerns about infertility and new evidence of risk of neurodevelopmental disorders in children of valproate-exposed fathers

In addition the group heard specific concerns about UK valproate prescribing:

- UK has high prescribing rates of valproate compared to most European countries
- Significant off-label valproate prescribing
- Male patients treated with valproate may not be aware of reproductive toxicities
- Lack of ongoing specialist oversight for many patients prescribed valproate

The CHM's advice is that valproate should only be used if there are no other effective or tolerated treatments, as agreed by two independent specialists. The aim of the new regulations is to make sure that valproate remains available to individuals who really need it — and to offer effective alternatives to those who do not.

The Valproate Stakeholder Network (VSN) has provided written feedback into the implementation group following a parallel session with MHRA. The VSN has raised concerns centred on the following themes:

- Tighter regulation of valproate prescribing could lead to an increase in epilepsy-related and bipolar disorder-related harms, including deaths
- Loss of autonomy in chronic relapsing conditions, with individuals being taken off valproate against their wishes
- Secondary impacts on epilepsy, neurology and mental health services
- Harms of valproate on the descendants of people with epilepsy

## Summary of advice

The implementation group has identified significant risks with implementation of the new regulations which need to be balanced against a reduction in reproductive harms. These risks can be divided into primary risks from changes in prescribing and secondary risks from pressure on healthcare systems. These risks differ between different populations. Overall, implementation of the new regulations will be logistically complex and should be approached in a phased manner. The issues and risks associated with each phase are identified below, together with advice on how the regulations could be implemented as safely as possible.

### Advice

A phased approach to implementation is recommended, with initial focus on introduction of the two-prescriber system in patients newly starting valproate. This will enable familiarity to be gained with the new system and for lessons to be learned for the more complex and riskier task of implementing new regulations in patients already established on valproate.

## **Implementation of new regulations in patients newly starting valproate**

### **How the two-prescriber system will work**

The implementation group noted that the two-prescriber requirement could result in delays if two face-to-face consultations were required for every patient. Second wet ink or electronic signatures could introduce delays and logistical problems.

### Advice

The group advised that two prescriber consultation could be performed by case discussion or review of notes. The group has provided definitions to the regulator as to how the term “independent specialist” should be interpreted.

### Advice

The details of the second signatory should be added to the ARAF by the first prescriber. A wet ink or electronic signature could introduce delays and is not needed if the second prescriber is identifiable. The second prescriber should be provided with a copy of the ARAF.

### Advice

Discussion of cases at multidisciplinary team (MDT) meetings should be able to substitute for the second signature, through a named representative of the MDT.

## **Clinical Guidance**

The implementation group observed that the phrase “no other effective or tolerated treatment” is difficult for clinicians and patients to interpret. The group noted that this phrase has been used in recent years to guide prescribing valproate in women of childbearing age and is interpreted alongside clinical guidelines. Clinical guidelines currently used include NICE/SIGN and *Pan College Guidance on Valproate Use*. For example, for treatment of generalised tonic-clonic seizures in women, this phrase is currently interpreted as meaning that lamotrigine and levetiracetam should be tried ahead of valproate.

### **Advice**

NICE/SIGN guidelines should be updated in light of the new regulatory position, and relevant new regulatory data made available to these bodies. Professional organisations (e.g. those contributing to the *Pan College Guidance on Valproate Use*) may also wish to produce their own advice to help guide prescribing decisions, or provide worked examples.

## **Female-specific considerations**

The new regulations do not introduce a major change to current clinical decision-making for women starting valproate.

## **Male-specific considerations**

In contrast, the new regulations introduce a substantial change to clinical decision-making for men starting valproate since reproductive risks in men are currently infrequently discussed. The implementation group notes the current concerns of the VSN regarding an absence of the final analysis of new clinical data regarding reproductive risks in men.

During the course of the implementation group meetings the group has viewed and discussed a new post authorisation safety study (PASS) mandated by the European Medicines Agency to look specifically at paternal risks of valproate exposure. This retrospective study across three Nordic registries reports a significantly increased risk of neurodevelopmental disorders in children whose fathers were exposed to valproate compared to levetiracetam/lamotrigine.

### **Advice**

As soon as legally/safely possible, the VSN and patients should be made aware of emerging concerns from the post authorisation safety study to address male reproductive risks. The views of the VSN on the risk-disproportionate nature of the regulations in men should then be reassessed and fed back to the implementation group. The manufacturer and owners of the PASS study should be encouraged to put the full results and analyses into public domain as soon as possible.

## **Educational materials**

The implementation group has provided input into the educational materials to support implementation, such as patient information leaflets and acknowledgement of risk forms (ARAFs). The ARAF has a specific purpose of documenting awareness and acknowledgement of reproductive risks. However, some group members feel this document is a limited tool to help guide the increasingly difficult conversations around drug choice in epilepsy and bipolar disorder. This is a particular issue for males where new risks are emerging which are associated with a level of uncertainty of their magnitude. It is also a particular issue for people with generalised epilepsies since the SANAD II RCT shows that other effective ASMs are inferior to valproate.

### **Advice**

There is important unmet need for early development of more rounded decision-making tools to help patients make informed choice which balance risks from epilepsy against risks from valproate (e.g. further development of NHSE decision tool developed with Winton Risk Communication Centre in 2021). Such tools will be optimally developed once important new data is in public domain, and with input from stakeholder groups.

## **Immediate capacity issues**

The phased implementation is intended to allow time to prepare healthcare systems to deal with the complex issue of offering alternatives to valproate to those already established on the drug.

## **Implementation in individuals already established on valproate**

### **General considerations**

The implementation group considers that the implementation of the new requirements is significantly more complex for patients already established on valproate. This is because (i) the clinical decision to change medication in a person successfully established on valproate is complex and (ii) patient numbers are higher and many men are not receiving annual specialist review. The implementation group strongly advises and supports the provision of adequate healthcare funds and staffing to support safe implementation. Inadequate resourcing of implementation has the potential to increase the risk of secondary harms arising from pressure on healthcare systems – replacing one safety problem with another.

There is a particular need for tools which improve efficiency of communication between patient, primary care, specialist 1 and specialist 2. The group considers digital tools to be central to the safe implementation. The group has met on two occasions to discuss the design of a digital ARAF, and to highlight the need for targeted investment in digital

infrastructure with the Parliamentary Under-Secretary of State for Mental Health and Women's Health Strategy.

### Advice

The UK Healthcare system should identify and provide adequate resource to support safe implementation. The group strongly supports the development and funding of a digital ARAF. The group notes that such digital tools should be web-based, linked with primary care and ideally be available across devolved nations.

### **Females already on valproate**

The implementation group notes that valproate clinical decision-making for women remains largely unchanged. Almost all female patients are under annual specialist care because of current regulatory requirements which include the need for a signed ARAF. The group agrees that the additional level of scrutiny of prescribing is reasonable given the very high levels of reproductive risks to women, combined with emerging concerns about transgenerational risks.

The implementation group discussed the reductions in valproate-exposed pregnancies following the introduction of the pregnancy prevention programme (PPP). Following introduction of the PPP there was a year-on-year fall in valproate-exposed pregnancies in England until 2021 when numbers have plateaued. Based on the experiences of group members using PPP in diverse populations, the group were of the view that continued pregnancies may in part be a reflection of stretched clinical services and challenges in reaching populations who struggle to access healthcare systems.

The group agreed that systematic and multidisciplinary assessment of valproate-exposed pregnancies would help better understand and address the reasons behind ongoing valproate-exposed pregnancies. The group also expressed the view that not all valproate exposed pregnancies represent a failure of risk mitigation. For example, a valproate-exposed pregnancy in a woman who has not been made aware of the reproductive risks should never occur. However, a pregnancy in a woman with high-risk valproate-responsive generalised epilepsy syndrome, who has mitigated and acknowledged reproductive risk (e.g. by reducing valproate dose to a minimum during pregnancy and signed an ARAF) may reflect high quality clinical care.

### Advice

There is a pressing need for detailed multidisciplinary assessment of valproate-exposed pregnancies, with feedback to improve care. A model for this is Maternal, Newborn and Infant Clinical Outcome Review Programme (MBRRACE)-UK report of Confidential Enquiries into Maternal Deaths and Morbidity where quality of care is

assessed at an individual patient level, and recommendations for improvement made in an iterative manner.

### **Males already on valproate**

The group recognises that for many men of reproductive age with migraine, bipolar disorder and focal seizures, there may be better therapeutic options than valproate. However, the main concerns of the group are focussed on the adverse events which could occur from switching people with generalised epilepsy syndromes away from valproate. This is because valproate is the most effective available treatment for generalised epilepsies, which represents about a third of people with epilepsy. Generalised seizures are associated with high epilepsy-related morbidity and mortality. Risks of switching these patients away from valproate to alternative effective anti-seizure medications (ASMs) include an increased risk of epilepsy-related harms including SUDEP and temporary loss of driving. These risks are not readily mitigated and will need to be balanced against emerging reproductive concerns at an individual patient level.

As such, careful and balanced explanation of overall benefit-risk will be required and informed patient choice needs to be at the heart of these decisions. The implementation group notes the strong concerns expressed from the VSN in this area, with particular concern about impacts on patient autonomy.

### **Audit, compliance and research**

The implementation group discussed how successful implementation could be defined and important gaps in knowledge that could be filled to support safe use of valproate in the future.

#### **Advice**

Defining success of the implementation of the new regulatory position should be based primarily on ensuring informed patient choice. All patients treated with valproate should be informed about benefits and risks, including new reproductive risks.

#### **Advice**

There should be a register of all patients on valproate.

#### **Advice**

The implementation group highlights the need to support research into further evaluating and quantifying emerging signals, in particular male and transgenerational



reproductive risks. There is also a need to identify the mechanisms of reproductive toxicity, in particular the role of HDAC inhibition and epigenetic change which could plausibly underpin the breadth of reproductive toxicities observed.

### **Summary of main recommendations for implementation of new regulatory position**

- Stakeholders should be made aware of emerging data
- Implementation of new regulations should be phased
- The two signature approach should be configured to minimise prescribing delays
- Clinical guidance is needed to interpret new regulations and should be updated
- MDTs should be used to support two prescriber decision-making
- More rounded decision-making tools should be developed with stakeholders when new data is made available
- Implementation should be adequately resourced, including digital ARAF
- Valproate exposed pregnancies should be evaluated in a multidisciplinary framework
- Further consideration should be given to flexibility of two prescriber system, especially to address stakeholder concerns about impacts on autonomy