



Medicines & Healthcare products
Regulatory Agency

Topiramate: review of safety in pregnancy

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

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1. Plain Language Summary

Key messages:

Topiramate (brand names Topamax, Topamax Sprinkle, Topiramate Accord, Topiramate Milpharm, Topiramate Cadila, Topiramate Crescent, Topiramate Glenmark, Topiramate Morningside, Topiramate Renata, Topiramate Rosemont, Topiramate Torrent, Topiramate Mylan, and Topiramate Zydus Pharmaceuticals UK) is approved in the UK to treat epilepsy and for the prevention of migraine. It is also sometimes used outside of the licence (off-label) to treat other conditions.

If topiramate is taken during pregnancy it can cause birth defects (such as cleft lip and/or palate or a malformation of the penis in baby boys (hypospadias)) and the baby may be born smaller and weigh less than expected. Due to these known risks, it has been recommended for some time that topiramate must not be used to prevent migraine during pregnancy and any patient taking topiramate for epilepsy and planning a pregnancy should make an appointment with their doctor for specialist review of their treatment. For all patients who can become pregnant it has also been recommended that they have a pregnancy test before starting topiramate and they use effective birth control (contraception) at all times when taking topiramate.

New data suggests that children of mothers who take topiramate during pregnancy may have an increased risk of mental development and learning problems, such as autism spectrum disorder and attention deficit hyperactivity disorder. Given these additional harms that topiramate may cause if taken during pregnancy, the Commission on Human Medicines (CHM) has advised that new measures should be introduced to minimise the risk of exposure of children to topiramate in the womb. For patients taking topiramate for the treatment of epilepsy, it is now recommended that topiramate should not be used during pregnancy unless there is no other suitable treatment. Also, regardless of the condition that topiramate is used for, in patients who are able to get pregnant they must use effective birth control (contraception) at all times during treatment and must follow the conditions/requirements of a Pregnancy Prevention Programme. This Pregnancy Prevention Programme aims to make sure that patients are fully aware of risks of topiramate use during pregnancy and agree to take steps to avoid becoming pregnant while taking topiramate. The full recommendations of the CHM are included in this report. The MHRA communicated this information to the UK public and healthcare professions in June 2024.

After their review, the CHM recommended the formation of an implementation group to advise on the introduction of the new measures into clinical practice. The implementation group included experts and representatives from across the healthcare system. They advised that the approach to implementation of the new safety measures, including a

Pregnancy Prevention Programme for topiramate, should aim to support safe and effective use of topiramate working within existing clinical practice for the management of epilepsy and migraine. The implementation group also advised on the content and format of the Educational Materials to support the Pregnancy Prevention Programme and endorsed the importance of seeking patient input on these materials.

If you are a patient on topiramate please discuss any concerns you have with your healthcare professional. Patients who are taking topiramate and are able to get pregnant must use effective birth control (contraception) at all times during treatment with topiramate. This is to reduce the risk of an unplanned pregnancy. Patients taking topiramate for epilepsy should not stop topiramate without advice from their healthcare professional. Suddenly stopping topiramate can be dangerous and may cause seizures to start again or happen more often or last longer than before.

Introduction to this report

The Medicines and Healthcare products Regulatory Agency (MHRA) 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 safety data conducted by the MHRA in 2022/2023, the advice of the CHM and the implementation group in 2023 and 2024, and the steps that the MHRA are taking to implement the new safety measures.

More information about this medicine

Topiramate is approved in the UK for the treatment of epilepsy in adults and children and also for the prevention of migraine headaches in adults.

Epilepsy is a common, long-term condition that affects the brain, causing repeated seizures. It can start at any age and can affect people throughout their lives. It is estimated that there are over a half a million people with epilepsy in the UK, which is around 1 in 100 people. There are many different types of epilepsy that have different causes. Most people with epilepsy take epilepsy medicines (also known as antiepileptic drugs or antiseizure medication), to stop their seizures from happening.

Migraine is a common long-term condition; it is estimated that over 10 million people in the UK suffer with migraine. Migraine is characterised by recurring, often disabling attacks of severe headache, nausea, vomiting, super-sensitivity to light and sound, along with other

signs and symptoms. There are multiple treatments available. The right treatment depends on the type of migraine, the symptoms experienced and how often the attacks occur and how bad they are. Migraine treatment usually includes acute treatment such as painkillers and anti-sickness medication to stop or shorten the attack. There are also preventive treatments, such as topiramate, which are taken daily to reduce how often the attacks occur, how long they last and how bad they are.

Reasons for the latest review and information considered

Topiramate is already known to harm a baby if it is taken during pregnancy – it is linked to an increased risk of birth defects and an increased risk of the baby being born smaller and weighing less than expected (small for gestational age). Therefore, it was already recommended that topiramate must not be used to prevent migraine in patients who are pregnant. Also, women should already have been advised to use effective birth control while on topiramate and to avoid becoming pregnant while taking this medicine.

Following a review by the CHM into the safety of antiepileptic drugs in pregnancy, including topiramate, in January 2021 we published new safety advice in [Drug Safety Update](#) with [patient advice](#), and a [Public Assessment Report](#). This included updated safety advice on topiramate.

At the time of the 2021 review, some data had raised concerns that topiramate use during pregnancy may be associated with an increased risk of autism spectrum disorder and poorer developmental outcomes. However, the numbers in the available studies were limited and further data were needed to reach firm conclusions.

Since then, new data has become available from observational studies suggesting a potential increased risk of autism spectrum disorder, attention deficit hyperactivity disorder and effects on learning development in children born to mothers who took topiramate during pregnancy.

Due to the new study data and data suggesting an increasing use of topiramate in women of childbearing age, a new safety review was started to assess the benefits and risks of topiramate and to consider whether further measures are required to reduce the risk of harm associated with topiramate use during pregnancy.

How the CHM reached their conclusions

At a number of meetings, the CHM considered the available evidence on the risks associated with the use of topiramate during pregnancy. This included information from published studies in humans and both published and unpublished studies in animals. The CHM was also presented with information summarised by the MHRA that fed back on

listening sessions that were held with individual patients where they were able to share their experiences with topiramate.

In reaching its conclusions and forming its advice, the CHM heard directly from experts, stakeholders and patient groups on the risks, how topiramate is used in clinical practice and the potential impact of the proposed regulatory measures.

Conclusions of the review

The CHM considered that the new data suggests that children of mothers who take topiramate during pregnancy may be at an increased risk of mental development and learning problems, such as autism spectrum disorder and attention deficit hyperactivity disorder. These new harms associated with use of topiramate during pregnancy are in addition to the known harms of a higher risk of a baby being born with birth defects and/or being born smaller and weighing less than expected at birth (small for gestational age).

The CHM noted the exposure data from the Medicines and Pregnancy Registry and the Clinical Practice Research Datalink, which suggested increasing use in female patients of childbearing age and a high number of pregnancies exposed to topiramate.

The CHM concluded that the exposure data and the serious harms that can occur to an unborn child if topiramate is taken during pregnancy, mean that further restrictions to the use of topiramate in patients who are able to get pregnant and in pregnancy are necessary. These restrictions are intended to avoid the use of topiramate in pregnancy, wherever possible. They should also ensure that any decision to start topiramate in a patient who can get pregnant should be made jointly by the patient and their healthcare professional and be informed by the benefits of treatment and also the serious harms to the unborn child associated with topiramate use during pregnancy.

Advice from CHM

Due to the known harms associated with the use of topiramate during pregnancy at the start of the review, it was already recommended that topiramate must not be used to prevent migraine in patients who are pregnant. The CHM recommended that the accumulating data strengthened the evidence that serious harms may occur if topiramate is used during pregnancy and a number of further measures were needed to minimise the risks.

In particular, the CHM recommended that the following additional restrictions to the use of topiramate were needed to avoid use during pregnancy, wherever possible:

- Patients who can get pregnant must use effective birth control (contraception) at all times while taking topiramate as part of a Pregnancy Prevention Programme.
- Topiramate must not be used to treat epilepsy in patients who are pregnant unless there is no other suitable treatment available to treat their condition.

The CHM advised that a Pregnancy Prevention Programme (PPP) should be introduced to avoid exposure of the unborn child to topiramate in the womb. The requirements of the PPP, which must be followed by any patient who can get pregnant, are to help ensure that patients who can become pregnant are fully aware of the risks of taking topiramate during pregnancy and the steps that need to be taken to avoid becoming pregnant while taking topiramate. The CHM recommended that educational materials for patients and healthcare professionals should be made available, to support the discussions between the patient and their healthcare professional about the risks and the pregnancy prevention measures.

Other measures recommended by the CHM are updates to the product information to fully reflect the available data on risks of use during pregnancy and include new information about the PPP and measures to be taken to reduce the risks. The CHM also advised that a visual warning symbol/pictogram is added to the carton of topiramate medicines. This symbol will show a pregnant woman in a red circle with a line through it and be accompanied by warning text about the risks.

The CHM's advice is presented in full in section 6.

Implementation advice for CHM recommendations

Following their review, the CHM established an implementation group to advise on the introduction of the new measures into clinical practice. This group, which included clinicians and representatives from the UK healthcare system, met a number of times in 2023 and 2024. The implementation group noted the CHM recommendation for the introduction of a PPP for topiramate. They stressed that introduction of a PPP would have a significant impact on clinical practice, particularly for migraine, which commonly occurs in women, and is usually managed in general practice. To support safe use of topiramate by patients and effective implementation of the PPP they advised that the approach should support the diagnosis and treatment of migraine and epilepsy in line with current clinical pathways and allow delivery through a multidisciplinary team.

The implementation group also advised on the content and format of the Educational Materials to support the PPP. They recommended that the aim should be for the materials to be as concise as possible avoiding unnecessary repetition and that separate versions of some materials should be provided for the epilepsy and migraine patient populations. They also advised that a digital version of the Annual Risk Awareness Form would help support

more effective implementation. The implementation group also advised on the approach to monitoring the impact of the new risk minimisation measures.

The MHRA also worked with Patient Charities and Organisations on the messages within the safety communications and the Educational Materials for patients, to ensure these were clear and would help patients to understand the risks and the actions needed to avoid exposure to topiramate during pregnancy.

Next steps

If you are a patient on topiramate please discuss any concerns you have with your healthcare professional. Patients who are taking topiramate and who are able to get pregnant must use effective birth control (contraception) at all times during treatment with topiramate. This is to reduce the risk of an unplanned pregnancy. Patients taking topiramate for epilepsy should not stop topiramate without advice from their healthcare professional. Suddenly stopping topiramate can be dangerous and may cause seizures to start again or happen more often and last longer than before.

The MHRA has issued a Drug Safety Update article to inform healthcare professionals of the new safety measures.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating 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.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

A Public Assessment Report was published in January 2021 following a comprehensive national review by the Commission on Human Medicines (CHM) into the safety of antiepileptic drugs in pregnancy. The CHM advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry.

The CHM review that was published in 2021 included the safety data that was available at that time in relation to use of topiramate in pregnancy. Since that review, new data has become available that raised concerns that topiramate use during pregnancy may be associated with an increased risk of autism spectrum disorder, attention deficit hyperactivity disorder and poorer learning developmental outcomes.

This report presents the MHRA's updated review of safety data relating to the use of topiramate in pregnancy and expert advice on management of risks, as advised on by the CHM. Changes have been made to the ordering and wording used in the original assessment report considered by the CHM to aid readability and to add context.

A glossary is provided for an explanation of the terms used in this report.

The information and assessments contained in this report reflect evidence that was available at the time of the review in 2022/2023. The MHRA and the CHM continues to monitor the safety and usage of topiramate closely, however the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Topiramate

Topiramate is a prescription only medicine that can be used:

- to prevent migraine headaches in adults after consideration of possible alternative treatment options. Topiramate is not intended for acute treatment of migraine
- alone to treat seizures (partial seizures with or without secondary generalised seizures) in adults and children over 6 years of age
- with other medicines to treat seizures (partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures) in adults and children aged 2 years and older and for the treatment of Lennox-Gastaut syndrome.

It is available as tablets, a liquid oral solution, or as capsules that can be swallowed whole or sprinkled on soft food. It is available as a number of different brand names, including Topamax, Topamax Sprinkle, Topiramate Accord, Topiramate Milpharm, Topiramate Cadila, Topiramate Crescent, Topiramate Glenmark, Topiramate Morningside, Topiramate Renata, Topiramate Rosemont, Topiramate Torrent, Topiramate Mylan and Topiramate Zydus Pharmaceuticals UK.

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown, but studies have identified a number of properties that may contribute to its efficacy.

One of the most important mechanisms underlying epilepsy and seizure activity is an excitation/inhibition imbalance caused by altered ion channel function and/or synaptic transmission (Staley K 2015, Shao R and others 2019). Numerous voltage- and ligand-gated ion channels are associated with a wide spectrum of epilepsies, giving rise to many potential therapeutic targets (Oyrer J and others 2018, Wei F and others 2017). Mechanisms by which antiepileptic drugs/antiseizure medicines are thought to act include 1) modulation of voltage-dependent sodium channels, which are responsible for regulating neuronal excitability throughout the central nervous system (CNS), 2) potentiation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), 3) modulation of voltage and receptor-gated calcium ion channels, which support processes including synaptic transmission and neuronal excitability in neurons, and 4) blockade of excitatory neurotransmission. Neurochemical and neurophysiological studies suggest that topiramate may act by all these mechanisms. Topiramate also inhibits some isoenzymes of carbonic anhydrase that are expressed in the brain and associated with epilepsy. However, the effect of topiramate is

much weaker than that of other well-known carbonic anhydrase inhibitors and hence this is not thought to be a key mechanism by which topiramate exerts its antiepileptic activity.

Antiepileptic drugs/antiseizure medicines are commonly used for the prophylaxis of migraine and possible modes of action may relate to general modulation of pain systems or more specifically to the systems involved in the pathophysiology of migraine (Silberstein 2008). As is the case for epilepsy, the efficacy of topiramate in migraine is likely to be due to multiple mechanisms, including modulation of voltage-dependent sodium and calcium channels, inhibition of the pathways involved in excitatory neurotransmission by glutamate, and stimulation of inhibitory neurotransmission by GABA. Topiramate has also been shown to suppress cortical spreading depression in a rat model, which is thought to be implicated in the pathophysiology of migraine aura. Overall, whether it is used in the treatment of epilepsy or the prevention of migraine, topiramate results in a reduction in excitatory transmission and increase in inhibitory neurotransmission.

3.2 Treatment of Epilepsy

Epilepsy is one of the most common neurological conditions that affects more than 70 million people worldwide (Roland and others 2019). It is estimated that just over nine people would have epilepsy in every 1,000 people each year. This means that more than 630,000 people are living with epilepsy in the UK (Wigglesworth and others 2023), so around 1 in 100 people. For around two-thirds of people with active epilepsy their epilepsy is adequately controlled by treatment with one or more antiepileptic drugs/antiseizure medications.

Guidance from the National Institute for Health and Care Excellence (NICE) recommends that topiramate can be used as monotherapy for myoclonic seizures and tonic or atonic seizures, and as adjunctive treatment in generalised tonic-clonic, focal seizures, and idiopathic generalised epilepsy. Where topiramate is recommended for use as monotherapy it is only recommended as a second- or third-line treatment, that is it should only be used after the initial treatment (first-line treatment) has failed, stopped working or has side effects that aren't tolerated.

Epilepsy is also one of the most common neurological conditions in pregnancy and it is estimated that around 2,500 infants are born to women with epilepsy every year in the UK (*UK Epilepsy and Pregnancy Register* [<http://www.epilepsyandpregnancy.co.uk/>]). About one-third of women with epilepsy are in the reproductive age group. The risks associated with the use of antiepileptic drugs during pregnancy are a significant concern for all women with epilepsy who are able to become pregnant. These risks need to be balanced against the risks of uncontrolled seizures both to the mother and the unborn baby. These discussions form an important part of the preconception counselling that should take place

between a woman who is planning to start a family and her specialist or general practitioner. It is also an important factor to be taken into consideration when initiating antiepileptic drug treatment in girls and women.

The NICE guidance (The Epilepsies: diagnosis and management Clinical guideline [CG137]) recommends that women and girls with epilepsy should be given information that is tailored to their age-specific and developmental needs. There should be regular review of the information that is provided about contraception, folic acid supplementation, conception, pregnancy, breastfeeding, caring for children and menopause.

Furthermore, there should be a discussion with women and girls who are able to become pregnant (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, concerning the risk of antiepileptic drugs/antiseizure medication causing malformations, neurodevelopmental impairments, and fetal growth restriction in an unborn baby. An assessment should also be made of the risks and benefits of treatment with individual antiepileptic drugs/antiseizure medication when prescribing for women and girls who are able to have children, now or in the future. This should include discussing the balance between the risks of poorly controlled seizures and the risks to the baby when antiseizure medicines are taken in pregnancy or while breastfeeding. It is recommended that the latest data on the risks to the unborn baby, including the MHRA safety advice on antiepileptic drugs/antiseizure medication in pregnancy, should be taken into consideration in decision making.

It is also recommended that regular (at least annual) monitoring reviews should be arranged for adults with epilepsy who are able to get pregnant and are taking valproate or any other high-risk teratogenic antiepileptic drugs/antiseizure medication and again reference to the MHRA safety advice on antiepileptic drugs/antiseizure medication in pregnancy is made.

3.3 Prevention of migraine

Migraine is a common condition with a global prevalence of around 1 in 7 people. This means that over a billion people worldwide get migraine and over 10 million in the UK. Migraine is characterised by recurring, often disabling attacks of severe headache, nausea, vomiting, super-sensitivity to light and sound, along with other mental, physical and psychological signs and symptoms. Most people have episodic migraine, although approximately 8% of people with migraine have chronic migraine (headache which occurs on at least 15 days per month and has the characteristics of a migraine on at least 8 days per month for greater than 3 months). It is estimated that 190,000 migraine attacks occur every day in the UK and that over three quarters of people who get migraine have at least one

attack each month. It is estimated people in the UK lose a total of 43 million days from their work and education each year because of migraine (The Work Foundation 2018).

The lifetime prevalence of migraine has been reported as 33% in women and 18% in men. Before puberty migraine is more common in boys than girls but this reverses at puberty with migraine affecting three times as many women as men. Migraine attacks can begin at any age but start typically in puberty and adolescence and rarely after 50 years of age.

Treatment for migraine falls into two categories: acute and preventive. Acute therapy is aimed at symptomatic treatment of the headache and other symptoms associated with an acute attack of migraine; it can include painkillers and anti-sickness medication to help stop or shorten the attack once it starts. Preventive medication is usually taken every day and aims to reduce the frequency, severity and duration of attacks.

NICE guidance (Headache in over 12s: diagnosis and management [CG150]) recommends topiramate, propranolol or amitriptyline first-line for the prophylaxis of migraine. It advises that there should be a discussion of the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life.

Migraine is common in women of reproductive age and may occur in pregnancy. In up to 80% of women who suffer migraines, both the frequency and severity of attacks improve during the second and third trimesters of pregnancy. However, in some cases migraine may fail to improve or worsen. In some women migraine presents for the first time during pregnancy.

Migraine itself does not appear to increase the risk of spontaneous abortion, congenital malformation or other pregnancy-related complications. However, if migraines are frequent or severe and left untreated, subsequent maternal effects such as dehydration, inadequate nutrition and stress may have an adverse effect on the fetus.

NICE guidance highlights that some preventive therapies are contraindicated in pregnancy. For topiramate, it states that the following should be discussed with women and girls of childbearing potential:

- the risk of fetal malformations
- the risk of reduced effectiveness of hormonal contraceptives
- the importance of effective contraception for women and girls of childbearing potential (for example, by using medroxyprogesterone acetate depot injection, an intrauterine method or combined hormonal contraceptive with a barrier method).

It also recommends that the MHRA safety advice on antiepileptic drugs/antiseizure medication in pregnancy is followed.

3.4 Harms of topiramate in pregnancy

The available data support that there is an increased risk of major congenital malformations in children born to women with epilepsy treated with antiepileptic drugs/antiseizure medications during pregnancy and that the risk is greater at higher doses of antiepileptic drugs/antiseizure medications and with polytherapy compared with monotherapy. It is also recognised that some antiepileptic drugs/antiseizure medications taken by a mother during pregnancy can affect the physical and mental development of the unborn baby. However, the type and level of risk associated with use of antiepileptic drugs/antiseizure medications during pregnancy differs according to the specific antiepileptic drug(s)/antiseizure medication(s) taken by the mother during the pregnancy.

Following a comprehensive national review by the CHM into the safety of antiepileptic drugs/antiseizure medications in pregnancy, including topiramate, in January 2021 we published new safety advice in [Drug Safety Update](#) with [patient advice](#), and a [Public Assessment Report](#).

The 2021 review showed topiramate exposure in-utero to be associated with an increased risk of congenital malformations (approximately 4 or 5 cases per 100 babies, compared with 2 or 3 in the general population). Topiramate was also shown to be associated with an increased risk of the baby being born of low birth weight and small for gestational age (fetal growth restriction).

At the time of the 2021 review, some data had raised concerns that topiramate use during pregnancy may be associated with an increased risk of autism spectrum disorder and poorer learning developmental outcomes. However, the numbers in the available studies were limited and further data were needed to reach firm conclusions.

The UK product information for topiramate, which was in place at the time of the 2021 review, contained the following safety advice relating to use in women of childbearing potential and in pregnancy.

Before initiation of topiramate in a patient who is able to get pregnant, pregnancy testing should be performed, and the patient should be fully informed of the risks if taken in pregnancy.

For epilepsy, alternative therapeutic options should be considered for patients who are able to get pregnant. If topiramate is used, a highly effective method of contraception is strongly

recommended, and the discussion with the patient should include information on both the risks associated with taking topiramate and of uncontrolled epilepsy during pregnancy.

For migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. Therefore, topiramate should not be taken to prevent migraine headaches by a patient who is pregnant. Also, as topiramate can affect how well certain methods of contraception work, it is recommended that a patient who is able to get pregnant talks to their doctor about the best method of contraception to use whilst taking topiramate.

3.5 Initiation of review in 2022

In 2022 new study data became available that also linked topiramate to an increased risk of [autism spectrum](#) disorders, and effects on learning and development in children exposed to topiramate during pregnancy. The CHM considered the findings from this study and advised that it provides robust evidence to support an association between prenatal exposure to topiramate and an increased risk of autism spectrum disorder, intellectual disability and the composite outcome of any neurodevelopmental disorder.

Information from the [Medicines and Pregnancy Registry](#), also suggested that total prescribing of topiramate was increasing, and it was one of the more commonly prescribed antiepileptic drugs/antiseizure medicines in women younger than 55 years of age, including during pregnancy. Information on the indications for use of topiramate are not available in this registry.

The MHRA started a further review to evaluate these findings in the context of the accumulating data (new and existing studies) relating to the benefits and risks of use of topiramate and the increasing prescribing of topiramate, with a particular focus on girls and women of childbearing potential and during pregnancy. The start of this review was communicated on [our website](#) and also through a [Drug Safety Update article](#). During the course of this review data from another study published in 2023 suggested that children whose mothers took topiramate during pregnancy had an increased risk of developing [attention deficit hyperactivity disorder](#).

3.6 Assessments considered by CHM

The CHM considered the available evidence relating to the safety of topiramate during pregnancy at its meetings in October and December 2022 and January and September 2023.

Data were considered from non-clinical and clinical studies that were either published in the scientific literature or were obtained from the topiramate marketing authorisation holders. These data included:

- non-clinical data on the reproductive toxicity of topiramate, effects on fertility, embryofetal toxicity, pre- and postnatal toxicity; and a specific focus on studies reporting toxicity to the developing nervous system
- clinical data on the risk of congenital malformations, neurodevelopmental disorders and other reproductive toxic effects on the fetus/neonate.

During the current review, the CHM was presented with a summary of the evidence that was evaluated as part of its earlier review in 2021. However, the focus of the current review was the more recent evidence that has become available since the findings of the 2021 review were published and the implications of this for the balance of benefits and risks of topiramate.

The CHM also considered information on patients' experiences with topiramate. This was informed by a small number of listening sessions held with patients living with epilepsy and also patients living with migraine and provided an invaluable opportunity to listen to the patient narrative and better understand their lived experiences.

The Medicines in Pregnancy Registry (NHS Digital, 2022 – now NHS England) and the Clinical Practice Research Datalink (CPRD) Aurum were interrogated to provide an overview of prescribing of topiramate and to obtain data on the number of women of childbearing age who were prescribed and dispensed topiramate, including during pregnancy.

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 topiramate 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 prevention of migraine).

The CHM also recommended that an expert working group be established to advise on the implementation of the PPP in clinical practice – the Topiramate Implementation Expert Working Group.

This report includes the recommendations of the CHM and the considerations of the Topiramate Implementation Expert Working Group.

4. Risks of topiramate in pregnancy

Congenital malformations

Data from non-clinical studies

Topiramate is a known teratogen in rodents and rabbits, inducing malformations in mice ($\geq 20\text{mg/kg/day}$), rats ($\geq 100\text{mg/kg}$) and rabbits ($\geq 120\text{mg/kg}$) at plasma concentrations relevant to human therapeutic doses. The spectrum of malformations induced varies depending on the species tested. Topiramate is an inhibitor of several isozymes of the enzyme carbonic anhydrase and induces the same characteristic abnormalities in the aforementioned species as that of other anhydrase inhibitors such as acetazolamide, therefore carbonic anhydrase inhibition appears to be the mechanism of teratogenicity.

Data from clinical studies

The clinical studies are mainly observational studies that have been conducted in pregnancy registers, national birth registers or healthcare databases. Given the nature of these data sources, it will be known that the patient was prescribed topiramate but it may not always be known what condition topiramate was being used to treat. Where the studies report findings or analyses according to the indication for use of topiramate this is presented but this information is not always available.

Data considered in 2021 review

The 2021 review considered data from meta-analyses (Weston and others 2016, Veroniki and others, 2017) and larger epidemiological studies in pregnancy registries (Hernandez-Diaz and others, 2012) and national birth registers (Kallen and others, 2013). These data supported an increased risk of major congenital malformations in children born to mothers who took topiramate during pregnancy compared with controls (unexposed women with or without epilepsy) and in comparison, with mothers who took lamotrigine or levetiracetam but not those who took carbamazepine, phenobarbital or phenytoin. With regards to risk of specific malformations, the available data suggest an increased risk of oral cleft lip or palate, hypospadias and atrial septal defect in association with topiramate. Overall, the data were supportive of a median prevalence of congenital malformations in babies of women taking topiramate of 4–5% and an increased risk compared with babies of unexposed women with or without epilepsy.

The risk of congenital malformations is greater when antiepileptic drugs/antiseizure medications are used as polytherapy compared with monotherapy. However, it is not always clear which of the individual antiepileptic drugs/antiseizure medications may be driving the increased polytherapy risk. Studies that examine the risk of congenital malformations associated with topiramate when used as part of polytherapy for epilepsy are limited. The [UK Epilepsy and Pregnancy Registry](#) (Hunt and others 2008) and [Australian Pregnancy Registry](#) (Vajda and others 2014, Vajda and others 2016) provide information on around 300 topiramate polytherapy exposed pregnancies in women with epilepsy and values reported for prevalence of congenital malformations ranged from 8-15% (mean value 12%), compared with a prevalence of 3% in unexposed controls in the Australian Pregnancy Registry. Data from the Australian Pregnancy Registry (Vajda and others 2014) also indicated a 3- to 4-fold increased risk of congenital malformations with topiramate polytherapy compared with unexposed pregnancies; there were fewer pregnancies exposed to topiramate monotherapy, which was not associated with an increased risk of congenital malformations. Malformation rates were statistically significantly increased in the polytherapy pregnancies (after excluding valproate) compared with the monotherapy pregnancies. A further analysis in the Australian Pregnancy Registry (Vajda and others 2016) showed that congenital malformation rates were similar in polytherapy pregnancies whether or not levetiracetam was included (7.14% vs. 8.38%) but were higher in polytherapy pregnancies involving topiramate compared with polytherapy excluding topiramate (14.94% vs. 6.55%: Odds Ratio 2.50, 95% CI 1.23–5.10). Whilst the number of studies examining the effect of polytherapy are limited, they do suggest an increased risk with antiepileptic drug/antiseizure medication polytherapy regimens that include topiramate and indicate that topiramate may be driving the increased risk seen with these regimens.

Some published studies have indicated a dose dependent risk of congenital malformations for topiramate, including a study in the Australian Pregnancy Registry (Vajda and others 2016) in which a statistically significant dose dependent association was observed for topiramate when used as part of polytherapy regimen (p value=0.025, $n=78$), but not topiramate monotherapy. The authors considered that this difference in risk may have correlated with an observed higher mean dosage of topiramate for polytherapy use; 247.7 ± 144.6 mg per day (median 200, range 25–700 mg/day) versus 186.9 ± 116.9 mg per day (median 113, range 6.25–400 mg/day) for monotherapy use. In a larger study in the US Medicaid database (Hernandez-Diaz and others 2018), a dose dependent increase in the risk of oral clefts (including cleft lip and palate) was observed; the adjusted risk ratios for daily doses of topiramate less than or equal to 100 mg and more than 100 mg were 1.64 (95% CI 0.53 to 5.07) and 5.16 (95% CI 1.94 to 13.73), respectively. Overall, the data are limited but suggestive of a dose-dependent effect of topiramate, but the available studies do not allow a threshold dose to be identified below which there is no risk.

Data available since 2021 review

Since the completion of the 2021 review, very few new studies have become available that inform our understanding of the risk of congenital malformations associated with the use of topiramate during pregnancy. Alsfook and colleagues (2021) conducted a retrospective study that evaluated the pregnancy outcomes in mothers with epilepsy who attended a tertiary care hospital in Saudi Arabia. In only 2 of the 85 pregnancies the mother took topiramate and in neither of these pregnancies the babies were born with congenital malformations. Vajda and colleagues (2021) examined data that was available up to May 2020 in the Australian Pregnancy Registry relating to pregnancies of women with epilepsy in which the presence or absence of fetal abnormality was known. The aim of this study was to examine the role of non-drug factors in relation to antiepileptic drug/antiseizure medication associated fetal malformations. Information on the prevalence and risk of congenital malformations was not reported from this study but the analyses suggested that dosage of topiramate was one of the factors that made a statistically significant contribution to the congenital malformation rate. Due to either the limited number of topiramate exposed pregnancies or the objectives of the study neither of these studies are considered to impact on the conclusions previously reached.

Cohen and colleagues (2023) examined pregnancies in the general population of the Nordic countries (Denmark 1997 to 2017, Finland 1996 to 2016, Iceland 2003 to 2017, Norway 2004 to 2022 and Sweden 2006 to 2019). Antiepileptic drug/antiseizure medication exposed pregnancies were defined as those in which the mother had filled one or more prescriptions for antiepileptic drugs/antiseizure medication (ATC code N03A) during the first trimester. The requirement for monotherapy was that the mother took only one antiepileptic drug/antiseizure medication substance from 90 days before her last menstrual period (LMP) to the end of the first trimester (primary analysis). A secondary (specific) exposure definition required at least two prescriptions to be filled during pregnancy, with at least one in the first trimester. The primary outcome was major congenital abnormalities diagnosed within 1 year of birth and recorded in the medical birth, patient, malformation or death register.

There were 15,906 pregnancies considered exposed to antiepileptic drug/antiseizure medication monotherapy including 8,339 to lamotrigine, 2,674 to carbamazepine, 2,031 to valproate, 1,313 to oxcarbazepine, 1,040 to levetiracetam, and 509 to topiramate. Epilepsy was the most common indication for each of the antiepileptic drug/antiseizure medication monotherapies. Of the antiepileptic drugs/antiseizure medications, topiramate was used least frequently for the treatment of epilepsy (in 47% of topiramate exposed pregnancies) and most frequently for the treatment of migraine (in 23% of topiramate exposed pregnancies). The other antiepileptic drug/antiseizure medication were prescribed more frequently for epilepsy (between 56% and 89.9% of exposed pregnancies) and infrequently for migraine (between 1.8% and 4.9% of exposed pregnancies).

Pregnancies exposed to antiepileptic drug/antiseizure medication monotherapy generally had a higher prevalence of any major congenital malformations than the antiepileptic drug/antiseizure medication-unexposed pregnancies. The highest prevalence of major congenital malformations was in those women exposed to valproate or topiramate during pregnancy with prevalence data ranging between 78.3 and 87.5 events per 1,000 pregnancies for valproate and 62.9 and 95.1 events per 1,000 pregnancies for topiramate. Compared to the unexposed population the prevalence rate of major congenital malformations for topiramate was 2-fold-higher in the primary analysis (3.04% vs. 6.29%) and 3-fold higher in the specific analysis (3.04% vs. 9.51%).

In this study cardiac, limb and multiple malformations were most frequently identified in association with topiramate monotherapy. However, the number of cases (n=32) reporting a major congenital malformation in association with topiramate is too small to identify a pattern of malformations.

Additionally, we were provided with some more recent data from UK Epilepsy and Pregnancy Register (UKEPR), which includes information on topiramate exposed pregnancies through to 31st March 2017 [Kinney and others 2017 personal correspondence]. Information is available on 145 pregnancies exposed to topiramate monotherapy. Of these, there were 127 live births with information on the outcomes - 113 normal births, 6 major congenital malformations (4.72%) and 8 minor congenital malformations (6.29%). The findings with regards to the rate of major congenital malformations is broadly consistent with that from an earlier dataset from the UK Epilepsy and Pregnancy Registry (Hunt and others 2008). These data also show that when valproate is used as part of the polytherapy along with topiramate the prevalence of major congenital malformations is statistically significantly greater (25.00% (8/32) [95% CI 13.03 to 42.33]) than when valproate is not included along with topiramate in polytherapy regimen (5.45% (11/202) [95% 2.96 to 9.59]).

Neurodevelopmental disorders and delay

Data from non-clinical studies

Data from non-clinical studies in rats published in the scientific literature reported some evidence of neurodegenerative changes in the brains of the offspring exposed during pregnancy (Glier and others 2004, Singh M, Mishra A., 2005, Kim 2007, Dag 2014, Hashish 2014, Liu 2015) and developmental neurotoxicity following post-natal administration to juvenile animals (Pavone 2003, Glier and others 2004, Kim 2007, Shi 2010, Liu 2015). The findings reported in the literature were not observed in the Good Laboratory Practice compliant studies which showed no clear evidence of neurodevelopmental toxicity apart from some behavioural changes in the rat embryofetal study. These behavioural changes were not considered to be treatment related and were not accompanied by histopathological

changes in the brain. There were some differences in study design between the regulatory compliant and non-regulatory compliant studies, which may explain the differences observed. These include the strains of rats used, routes of administration employed and stage of pregnancy when dosing was initiated.

Overall, based on the data available the potential for topiramate to induce adverse effects on the developing nervous system cannot be ruled out. No conclusions can be drawn on the mechanism of toxicity at present.

Data from clinical studies

The clinical studies are mainly observational studies that have been conducted in pregnancy registers, national birth registers or healthcare databases. Given the nature of these data sources, it will be known that the patient was prescribed topiramate but it may not always be known what condition topiramate was being used to treat. Where the studies report findings or analyses according to the indication for use of topiramate this is presented but this information is not always available.

Data considered in 2021 review

Neurodevelopment covers a range of different functions including intellectual abilities, language abilities, motor function, social functioning, memory and attention skills and also covers symptoms that form the clinical diagnoses of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD).

At the time of the 2021 review, there were very limited clinical data available to inform on the effect of topiramate exposure during pregnancy and the risk of neurodevelopmental disorders in the offspring. Bromley and colleagues (2016) conducted a cross-sectional observational study that retrospectively enrolled children from the UK Epilepsy and Pregnancy Registry. Mother–infant pairs were eligible for inclusion if the infant had been a live birth between September 2004 and May 2007 and mothers were taking antiepileptic drug/antiseizure medication monotherapy or they were untreated during their pregnancy. Assessor blinded neuropsychological assessments were conducted between 5 and 9 years of age. The mean topiramate dose was 271.3 mg/day (range 50 to 800) and the mean age at assessment for topiramate was 76.7 months (SD 13). This study reported on data for 27 children who had prenatal exposure to topiramate, and the findings did not suggest reductions in the cognitive abilities of the children. Prenatal exposure to topiramate was not associated with reductions in child cognitive abilities, including Full Scale (FS) IQ (-0.4, 95% CI -9.7 to 8.9; p=0.44), verbal abilities (-6.4, 95% CI -15.6 to 2.8; p=0.17), performance abilities (-0.9, 95% CI -10.9 to 9.1; p=0.86), or processing speed (4.8, 95% CI -1.0 to 10.7; p=0.10). Comparable IQ scores were seen in the groups at 5 to 9 years of age (FSIQ mean (SD) – Topiramate 100.5 (13.2) vs Control 99.7 (13.6)).

Knight and colleagues (2020) conducted an observational, cross-sectional study that retrospectively enrolled children from the UK Epilepsy and Pregnancy Registry. Mother-child pairs were eligible for inclusion if the child had been a live birth and was up to 17 years of age at the time of participation and the mothers had epilepsy that was either being treated with topiramate during pregnancy or they were untreated during pregnancy. Due to recruitment issues, comparisons were made to a VABS=III normative sample (n=2560). Adaptive behaviour data was available for 21 children in the topiramate group. Compared to the normative sample, topiramate exposed children had poorer levels of adaptive behaviour with significantly lower mean scores in global Adaptive Behaviour Composite (ABC) (unadjusted mean = 91.10, $p = 0.023$). The effects of topiramate dose were explored (low dose = ≤ 200 mg/day, high dose = > 200 mg/day) and the results suggest that, even after adjustment for parental higher education, there was a significant negative association between topiramate dose and ABC scores. Similar dose-response relationships were observed for communication domain scores and socialisation domain scores. Knight and colleagues also observed statistically significantly lower mean scores for daily living skills (unadjusted mean = 90.38, $p = 0.003$) and socialisation skills (unadjusted mean = 90.86, $p = 0.028$) in the topiramate group compared with the normative sample. A total of four of the topiramate exposed children (19.05%) had diagnoses of autism spectrum disorder. The observed incidence of autism spectrum disorder in the topiramate group was significantly higher than estimates of UK prevalence rates for autism spectrum disorder (19.05% vs 1.1% $p < 0.001$).

The cross-sectional observational studies by Bromley and colleagues and Knight and colleagues have a number of strengths, including prospective collection of the pregnancy details, blinded standardized neuropsychological assessment, the collection and control for a number of influential covariates, assessment of school-age child IQ and exploration of effect of antiepileptic drug/antiseizure medication dose. The design also means that it is possible to detect differences with a much smaller cohort, however, the size of the topiramate cohorts in both studies mean that only large effect sizes would be detectable. Consequently, the results of the study by Bromley and colleagues should be interpreted with caution as this study would not be adequately powered to detect smaller differences in neurodevelopment. Also, the lack of an unexposed control group is an important limitation of the study by Knight and colleagues as this may result in possible confounding due to baseline differences between the two groups. Overall, considering the strengths and limitations of these two studies, it was considered that they did not allow definitive conclusions to be reached about the effects of topiramate and further studies would be needed to confirm these findings.

Other studies considered during the 2021 review examined the effects of topiramate on cognitive, motor and behavioural outcomes (Rihtman and others 2012), autistic traits (Bjørk and others 2018), learning disabilities (Bech and others 2018) and language impairment (Husebye and others 2020). These studies all included very small cohorts of topiramate exposed children ($n \leq 10$) and reported mixed results. Given the small numbers in these

studies it was considered that they do not allow firm conclusions to be reached with regards to effect of exposure to topiramate in pregnancy on the neurodevelopment of the children. Furthermore, the aim of the study by Bjørk and others (2018) was to examine whether folic acid supplementation and folate status in pregnancy are associated with reduced risk of autistic traits owing to antiepileptic drug/antiseizure medication exposure in pregnancy and hence was limited in terms of what it could inform on the risk of autistic traits in association with specific antiepileptic drugs/antiseizure medications.

Data available since 2021 review

A number of studies have become available since the completion of the 2021 review and include some relatively large cohort studies (Blotière and others 2020, Bjørk and others 2022, Hernandez-Diaz and others 2022 and Dreier and others 2023)

Blotière and colleagues 2020

The study by Blotière and colleagues is a large, reasonably well-conducted nationwide population-based cohort study that analysed data from two well-established French healthcare databases. It examined children born alive between 2011 and 2014 and exposed prenatally to antiepileptic drug/antiseizure medication monotherapy. Women were considered to be exposed during pregnancy when an antiepileptic drug/antiseizure medication had been dispensed between 30 days before the beginning of pregnancy and the end of pregnancy.). A total of 477 children were exposed to topiramate monotherapy and compared with 2916 children exposed to lamotrigine monotherapy.

This study found a comparable risk of neurodevelopmental disorders and speech therapy requirements between topiramate exposed and lamotrigine exposed children - neurodevelopmental disorders adjusted hazard ratio 0.8 (95% CI 0.4 to 1.9) and speech therapy adjusted hazard ratio 1.2 (95% CI 0.8 to 1.8). Exposure to topiramate was not associated with a statistically significant increase in risk of any of the other outcomes measured including: pervasive developmental disorders - adjusted hazard ratio 0.3 (95% CI 0.0 to 4.9) and “mental retardation” (term reflects terminology used by study authors) - adjusted hazard ratio 0.5 (95% CI 0.1 to 3.3). It is of note that the median duration of follow-up in this study is relatively short (topiramate group 3.6 years (range 2.6 to 4.6)) and hence this study may only have identified the more severe disorders that are diagnosed earlier. A number of sensitivity analyses were conducted, the findings of which were similar to those of the main analysis. One of the sensitivity analyses restricted the study population to women treated for epilepsy. For this analysis, topiramate was no longer included in the data presented suggesting that there was little or no use of topiramate monotherapy in women with epilepsy.

Blotière and colleagues used statistical methods to reduce confounding and adjusted for sociodemographic factors (maternal age at birth, eligibility for CMU-C-complementary universal health insurance) mother's use of folic acid, SSRIs and antipsychotics, and maternal history of mental and behavioural disorders. There is an absence of information on several other potential confounding factors including maternal education and IQ, and paternal and family data on neurodevelopmental disorders. Therefore, the possibility of residual confounding exists. The outcomes were those recorded in hospital so this study would likely only identify severe cases and it does not inform on subdiagnostic level symptoms that may still influence daily functioning.

Bjørk and colleagues 2022

The study by Bjørk and colleagues is a large, well-conducted study using established data sources from 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), which is part of the Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) infrastructure. Data from around 4.5 million mother-child pairs were examined and this included 24,825 children (0.6%) who were prenatally exposed to antiepileptic drugs/antiseizure medications (at least 1 antiepileptic drug/antiseizure medication from last menstrual period till birth). Of the children prenatally exposed to antiepileptic drugs/antiseizure medications, 16,170 were born to mothers who had epilepsy. Information was available for 471 children who were prenatally exposed to topiramate monotherapy of which 246 were born to women with epilepsy.

Crude incidence rates and crude cumulative incidence of autism spectrum disorder, intellectual disability and a composite of neurodevelopment disorders by age 8 years were calculated. These were based on specific ICD-10 codes and positive predictive values i.e. likelihood of identifying true cases of autism spectrum disorders diagnosis in Nordic health registers is high (86% to 90%). Hazard ratios were adjusted for various confounders, which included birth year, child's sex, maternal characteristics – age, parity, birth country, marital status, education, concurrent antidepressant or opioid use, depression, anxiety, personality disorders, number of somatic diagnoses, hospitalisation in year preceding pregnancy. The median age at the end of follow-up was 8 (range 4.0 to 12.1) years and the mean age at diagnosis was between 6.1 and 7.9 years across all countries; for topiramate the median follow-up time was 5.7 years (range 2.9 to 9.1).

In unexposed children of mothers with epilepsy, the 8-year cumulative incidence of autism spectrum disorder and intellectual disability were 1.5% and 0.8% respectively compared with 4.3% and 3.1% in children of mothers with epilepsy exposed to topiramate monotherapy. The adjusted hazard ratios for autism spectrum disorder and intellectual disability were 2.8 (95% CI 1.4 to 5.7) and 3.5 (95% CI 1.4 to 8.6). There was also an increased risk of any neurodevelopmental disorder in children of mothers with epilepsy exposed to topiramate

compared with children of mothers with epilepsy not exposed to antiepileptic drugs/antiseizure medication – adjusted hazard ratio 2.13 (95% CI 1.1 to 4.0).

In unexposed children of mothers from the total population, the 8-year cumulative incidence of autism spectrum disorder and intellectual disability were 0.8% and 0.3% respectively compared with 3.3% and 2.0% in children of mothers from the total population exposed to topiramate monotherapy. The adjusted hazard ratios for autism spectrum disorder and intellectual disability were 2.64 (95% CI 1.5 to 4.7) and 3.9 (95% CI 1.8 to 8.7). In the total population, there was also an increased risk of any neurodevelopmental disorder in children of mothers exposed to topiramate compared with children of mothers not exposed to antiepileptic drugs/antiseizure medication – adjusted hazard ratio 2.29 (95% CI 1.4 to 3.7).

Both valproate and topiramate were associated with a dose-related risk of the combined outcome of any neurodevelopmental disorder. For topiramate at doses less than 100mg per day the adjusted hazard ratio was 1.7 (95% CI 1.0 to 2.8) while for doses of 100mg per day or more the adjusted hazard ratio was 2.9 (95% CI 1.3 to 6.6). For valproate the adjusted hazard ratio was 2.3 (95% 1.9 to 2.8) for doses less than 750mg per day and there was an adjusted hazard ratio of 5.6 (95% CI 4.7 to 6.8) for doses of 750mg or more per day. There was minimal or no dose-related risk for the other antiepileptic drugs/antiseizure medication.

A range of well thought through sensitivity analyses were also conducted. Across most of the different analyses, topiramate and valproate showed statistically significant effect estimates of a greater than 2-fold increased risk for autism spectrum disorder and intellectual disability or the combined outcome of neurodevelopmental disorders, mainly compared with children from the general population.

Whilst there are several limitations of the study, these were not considered to negate its findings. One limitation is that the clinicians were not blinded to the exposure history of the child, which could have impacted the diagnostic process. Another limitation is that the data available in the Nordic registers did not inform on subdiagnostic level symptoms, which may mean that the study may only have identified the more severe disorders. The relatively small number of exposed cases for topiramate was also considered to result in greater uncertainty, as reflected in the wider confidence intervals. There was, however, some divergence from the other antiepileptic drugs/antiseizure medications that were included in the study and where the data did not support an increased risk of neurodevelopmental disorders. There also remained the possibility of residual confounding, however, it is considered that the magnitude of this would need to be quite large to explain the effect estimates that have consistently been observed for topiramate and valproate. Hernandez-Diaz and colleagues 2022

Preliminary findings, from a large cohort study nested in two US healthcare claims databases; the Medicaid Analytic eXtract database (public insurance) and the IBM Health

MarketScan database (private insurance) were presented at the Annual Conference of the International Society for Pharmacoepidemiology in 2022 (the International Conference on Pharmacoepidemiology and Therapeutic Risk Management – ICPE). Therefore, the limited information about this study, which is presented below, is based on what was presented at the ICPE conference. At the time of the review there was not access to any information on further analyses that the authors would have conducted but further data have since been published (Hernandez Diaz and others 2024).

Exposure to specific antiepileptic drugs/antiseizure medication was defined based on one or more prescription fills from gestational week 19 until delivery. Cumulative incidence of neurodevelopmental disorders by 8 years of life was estimated. Hazard ratios were estimated with propensity score weighting to adjust for various confounders and estimates were combined from both the data sources, to give pooled results. Pregnancies exposed to topiramate (n=2,063; 45.5% had epilepsy diagnosis) were compared with pregnancies unexposed to antiepileptic drugs/antiseizure medication (n=3,279,279) and also to pregnancies exposed to lamotrigine (n=4,316; 43.8% epilepsy diagnosis).

Preliminary information from this study showed that by 8 years of age, children prenatally exposed to topiramate had a higher risk of neurodevelopmental disorders compared to the unexposed group (pooled adjusted hazard ratio 1.26, (95% CI 1.05 to 1.52)) but not relative to children born to women with epilepsy (adjusted hazard ratio 1.19 (95% CI 0.85 to 1.68)) or to children prenatally exposed to lamotrigine (adjusted hazard ratio 1.10 (95% CI 0.91 to 1.34)).

The study by Hernandez-Diaz and colleagues (2022) involves the largest cohort of topiramate exposed pregnancies to date (n=2,063) and used algorithms to identify diagnoses of neurodevelopmental disorders that have previously been validated in others claims-based databases and been found to have a high likelihood of identifying true cases of neurodevelopmental disorders (Straub and others 2022). The authors suggest that the increased risk seen with topiramate compared with the general population is largely explained by the indications and other related factors. An important limitation of this study is that Hernandez-Diaz and colleagues presented pooled hazard ratios. Such an approach mixes different populations of publicly and privately insured patients and hence careful consideration needs to be given when interpreting results obtained from combining results from the two healthcare claims databases. Furthermore, due to the differences in the populations covered in the two US databases, whether the results could be applied to the UK population should be considered.

There is possibility of residual confounding as it is not clear whether parental covariates, such as maternal education, IQ, and paternal characteristics were considered or even available in the databases. In terms of outcomes, the ICD codes used might not fully capture broader symptoms. Hence, it is likely that data was not available on subdiagnostic level

symptoms that may still have an effect on daily functioning. Therefore, the results could underrepresent the extent of the risks associated with prenatal exposure.

Since the completion of the review, the full results of this study have been published (Hernandez-Diaz and others 2024), which include updated numbers for exposures to topiramate and the analyses focus on the risk of autism spectrum disorder. The full results showed that by 8 years of age, children prenatally exposed to topiramate had a higher risk of autism spectrum disorder compared to the unexposed group (pooled adjusted hazard ratio 2.17, 95% CI 1.54 to 3.07) but not relative to children born to women with epilepsy (adjusted hazard ratio 0.96, 95% CI 0.56 to 1.65) or to children prenatally exposed to lamotrigine (adjusted hazard ratio 1.22, 95% CI 0.76 to 1.98).

Dreier and colleagues 2023

The study by Dreier and colleagues, was conducted by the same investigators who conducted the study by Bjørk and colleagues (2022). They shared several similarities including design (prospective, population-based register study) and data source (within the SCAN-AED project using Nordic register infrastructure). Prenatal exposure to antiepileptic drugs/antiseizure medication was defined as maternal prescription fills from 30 days before the first day of the last menstrual period until birth and so employed a broader exposure window than that of the study by Bjørk and colleagues. Children were considered to have a psychiatric or neurodevelopmental disorder if they were registered with any main or secondary diagnosis from the ICD-10 F chapter (excluding F00-09).

A total of 38,661 children of mothers with epilepsy were identified, who were followed up to 22 years of age (mean [Standard Deviation] age 7.5 [4.6] years). For topiramate 290 children of mothers with epilepsy were followed-up for an average of 7 years (mean [Standard Deviation] follow-up - 7.0 [3.7] years). Children of mothers with epilepsy unexposed to antiepileptic drugs/antiseizure medication had a 31.3% (95% CI: 28.9% to 33.6%) risk of being diagnosed with a psychiatric disorder (combined endpoint) by 18 years of age, whereas the corresponding risk was 42.1% (95% CI: 38.2% to 45.5%) for valproate monotherapy exposure. Due to insufficient follow-up, the cumulative incidence of psychiatric disorders at the age of 18 was not provided for topiramate. However, at the age of 10 years 20.4% of children of mothers with epilepsy exposed to topiramate had a risk of being diagnosed with a psychiatric disorder compared to 13.9% of children of mothers with epilepsy not exposed to antiepileptic drugs/antiseizure medication and 27.2% of children of mothers with epilepsy exposed to valproate.

The number of children of mothers who took topiramate during pregnancy was lower than in the other studies (n = 290). However, the study supports an increased risk of attention deficit hyperactivity disorder (ADHD) (adjusted hazard ratio, 2.38; 95%CI, 1.40 to 4.06) with topiramate and potentially an increased risk of intellectual disability (adjusted hazard ratio,

2.23; 95% CI, 0.90 to 5.50) and autism spectrum disorder (ASD) (adjusted hazard ratio, 1.93; 95% CI, 0.95 to 3.94). The authors consider that the lack of statistical significance of the increased risk of intellectual disability and autism spectrum disorder in this study may reflect that a broader exposure window was used (from 30 days before the first day of the last menstrual period until birth). They consider that a narrower exposure window (as was used in the study by Bjørk and others – from last menstrual period until birth) may better capture cases with actual exposure to topiramate during pregnancy.

The authors also conducted analyses that restricted the population to 25,139 children of mothers with active epilepsy, of whom 15,378 (61.2%) were prenatally exposed to antiepileptic drugs/antiseizure medication. Generally, this did not substantially change associations with the combined psychiatric end point, however, it did make the association with topiramate stronger (adjusted hazard ratio, 1.60; 95%CI, 1.11 to 2.29, compared with the main cohort/unrestricted population adjusted hazard ratio 1.34; 95%CI 0.94 to 1.90).

Reproductive toxic effects on the fetus or neonate

Data from non-clinical studies

Intrauterine growth restriction and reduced bodyweights are a known effect of topiramate. Reductions in offspring weights and/or delays in ossification were reported in the Good Laboratory Practice compliant developmental and reproductive toxicity studies in mice, rats and rabbits. In addition, reductions in the parental weights were observed in almost all of the studies which often correlated with decreases in food consumption. Delays in physical developmental signs following pre- and postnatal exposures were also associated with reductions in bodyweight gains postnatally and low birthweights in the rat. The weight lowering effect of topiramate was also evident in the juvenile rat toxicology study.

Fetal weights and skeletal ossification were also reduced at 500 mg/kg/day in conjunction with maternal toxicity (decreased mean bodyweight and bodyweight gain, increase in intrauterine death as the intermediate and high dose).

The mechanism for the intrauterine growth restrictions is unclear. However, the data from regulatory compliant studies and the published scientific literature suggest that intrauterine growth retardation is likely to be related to effects on maternal bodyweights and bodyweight gain and potentially also involve a direct effect on the placenta.

Data from clinical studies

Data considered during 2021 review

Data from the North American Antiepileptic Drug Pregnancy Registry (Hernandez Diaz and others 2017) as well as studies in Danish and Norwegian population birth registers (Killic and

others 2014, Veiby and others 2014) indicate an approximate 2- to 3-fold increased prevalence of babies born small for their gestational age following exposure to topiramate during pregnancy compared with unexposed pregnancies or pregnancies exposed to lamotrigine. These data are supported by a meta-analysis by Veroniki et al, 2017. Two smaller epidemiological studies (Hunt and others 2008 and Wade, 2015) did not show an increased relative risk of small for gestational age, however, these are smaller studies that may not have been adequately powered to detect an increase in risk and/or where potential confounding factors may not have been fully adjusted for in the analyses.

Some studies suggest that the prevalence of small for gestational age in babies exposed to topiramate is highest amongst the antiepileptic drugs/antiseizure medications studied (Veiby and others 2014) and that the risk with topiramate is approximately 2.4-fold greater than that with lamotrigine (Hernandez Diaz and others 2017). There are also some, albeit limited, data on the effects of dose that suggest a higher prevalence of small for gestational age with higher doses of topiramate, but this was not statistically significant.

The available clinical data examining the effect of topiramate on fetal loss are very limited and the findings are inconsistent (Ornoy and others 2008, Trivedi and others 2018, Vajda and others 2018, Veroniki and others 2017). The studies contain limited numbers of topiramate exposed pregnancies and for the studies that suggest an increased risk it is considered that the results may be affected by confounding.

Similarly, the available clinical data on the effects of topiramate on preterm birth are very limited; the meta-analysis by Veroniki and colleagues 2017, a study in the North American Antiepileptic Drug Pregnancy Registry (Hernandez-Diaz and others 2014) and a study by Ornoy and colleagues 2008 do not suggest an increased risk but given the limited data, no firm conclusions can be reached.

Data available since 2021 review

Since the completion of the 2021 review, data has been published from the multicentre Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study (Van Marter and others 2021) being conducted in the US. This study examines whether growth measures at birth differ between babies of women with epilepsy compared with a group of pregnant women without epilepsy. A total of 331 pregnant women with epilepsy delivered 345 infants (7 pairs of twins) and 102 pregnant women without epilepsy delivered 106 infants (2 pairs of twins). The analyses in this study showed generally favourable neonatal outcomes among pregnant women with epilepsy compared with those without epilepsy. The exceptions were for topiramate monotherapy, which was associated with substantially lower birth weight z score than other monotherapies (mean \pm SD: -1.23 ± 0.32 , $n=4$) and oxcarbazepine which was associated with a greater likelihood of neonatal intensive care unit or special care nursery admission than other monotherapies. Due to the small number of

topiramate exposed pregnancies the study authors advise that the results should be interpreted with caution. However, these findings for topiramate are consistent with those seen in other studies in the North American Antiepileptic Drug Registry (Hernandez-Diaz and others 2014, Hernandez Diaz and others 2017) and the Norwegian birth register (Veiby and others 2014), which suggest that exposure to topiramate monotherapy during pregnancy is associated with babies being born at lower birthweights.

Exposure data

Data on the use of topiramate at patient-level in England is based on the Medicines and Pregnancy Registry (NHS Digital, 2022 – now NHS England) and Clinical Practice Research Datalink (CPRD) Aurum data. The Medicines and Pregnancy Registry provides data on the number of women of childbearing age who were prescribed and dispensed topiramate in the community in England, including during pregnancy. The CPRD Aurum analysis provides data on the prevalence and incidence rates of topiramate prescribing in England, including possible indications of prescribing. Proportions of women prescribed topiramate during pregnancy by the possible main indications (migraine and epilepsy) is also presented.

Medicines and Pregnancy Registry

In 2021 and 2022, the MHRA funded NHS Digital (now NHS England) 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 antiepileptic drugs/antiseizure medication who become pregnant should be developed. The registry contains linked data from three NHS England wide patient-level datasets; [NHS Business Services Authority \(NHSBSA\) prescribing data](#) for medicines dispensed in primary care, the [Maternity Services Data Set \(MSDS\)](#), and [Hospital Episodes Statistics \(HES\)](#). Healthcare professionals do not proactively enter their patients for the registry. The registry captures data on the use of the more commonly used antiepileptic drugs/antiseizure medications, however, the information captured includes use in epilepsy as well as other indications. Information on the indication for use is not available in this registry.

A report from the registry that contained data from April 2018 to March 2022 showed that:

- A total of 111,197 females aged 0 to 54 years were prescribed topiramate on one or more occasion between April 2018 and March 2022.
- The number of females aged 0 to 54 years who were prescribed topiramate in March 2022 was 31,278.

- The number of younger females prescribed topiramate is steadily increasing. Of the 31,278 females prescribed topiramate in March 2022, 18,341 were aged 16 to 44 years.
- There has been an increase of 7,975 (34%) in the number of females prescribed topiramate in a month from April 2018 to March 2022.
- There were slight fluctuations in the number of new starters of topiramate during the time period of the registry. For example, the number of new starters of topiramate, in March 2022 was 1,956 which was a reduction of 5% from 2,055 in March 2021.
- A total of 1,665 females were prescribed topiramate during pregnancy between April 2018 and March 2022; There were slight fluctuations in the number of females exposed to topiramate during pregnancy over 6-month periods in the registry, ranging from 203 females between October 2018 and March 2018 to 226 females between October 2021 and March 2022. 160 females were exposed to topiramate during pregnancy between April 2018 and September 2018.
- A total of 287 females started their prescription of topiramate during pregnancy (they had not been dispensed topiramate in the preceding 12 months).

Clinical Practice Research Datalink (CPRD) Aurum

The CPRD Aurum primary care database, which contains anonymised longitudinal records of patients registered with contributing primary care (GP) practices across England, was used to estimate topiramate prescribing.

In CPRD Aurum, 85,434 patients (all ages) had received at least one prescription of topiramate from 1 January 2010 to 31 December 2021. Out of these 62,194 patients had their first ever topiramate prescription in the study period. Around 73% (n=62,529) of the total prevalent cohort of the patients were female. During the study period the highest frequency of prescribing was in 16- to 44-year-olds (54%, n=46,426). Prevalence and incidence prescribing rates were calculated per quarter and patients were eligible for inclusion for each 3-month period if they were alive and in active follow-up for the whole quarter (n=83,271; 73% females; 54% 16 to 44 years).

There were 1,806 pregnant women (2,377 pregnancies) who had at least one topiramate prescription during pregnancy from 1 January 2010 to 31 December 2021.

Key findings from the CPRD Aurum quarterly prescribing rates analyses are presented below. Of note, indication of a medication is not directly linked to a prescription record in CPRD. Hence assumptions have to be made when assessing possible reasons for prescribing a particular medicine to infer what indication could be. This is done by reviewing

patient medical histories in CPRD. Therefore, the following are estimates since assumptions had to be made especially regarding indications.

- Over 75% of patients aged 16 to 44 years prescribed topiramate are female.
- New prescriptions of topiramate are occurring at a reasonably constant rate with the highest rate of new prescriptions in females aged 16 to 44 years and 45 to 54 years.
- The most common indication for a prescription of topiramate is migraine prophylaxis. In recent years, approximately 4 to 5 times the number of females aged 16 to 44 prescribed topiramate have a record of migraine or headache compared to epilepsy or seizure. Prescribing in patients with epilepsy in this age group has remained constant over recent years.
- During pregnancy, roughly one half of women are prescribed topiramate for migraine prophylaxis or headache and just over 40% are prescribed topiramate for epilepsy or seizure (for the remainder these two indications are not recorded/indication is not known).

5. Discussions and Conclusions

Congenital Malformations

The currently available data from meta-analyses (Weston and others 2016, Veroniki and others 2017), studies in pregnancy registries (Hernandez-Diaz and others 2012, Kinney and others 2017) and national birth registers/linked healthcare registers (Kallen and others 2013, Cohen and others 2023) show that topiramate use during pregnancy is associated with an increased risk of congenital malformations.

At the time of the 2021 CHM review, the available studies suggested a median prevalence of major congenital malformations with topiramate exposure of 4.3% (range 1.5% to 12.2%), and this was higher than that in the control groups (median 3.1%, range 2.4% to 3.4%) and the known background rate in the general population of 2% to 3%. The studies support an increased risk of congenital malformations in children born to mothers who took topiramate during pregnancy compared with controls (3- to 4-fold higher than unexposed women with or without epilepsy) and compared with mothers who took lamotrigine or levetiracetam (~2-fold higher). The prevalence and magnitude of the risk of major congenital malformations from these studies were broadly in line with what was already included in the topiramate product information for patients and healthcare professionals.

The new Nordic-register based study by Cohen and colleagues is a large, reasonably well-conducted study that provides information on a relatively large number of topiramate exposed pregnancies. The findings of this study are consistent with what is known about the relative increased risk of major congenital malformations – that is a 2-to-3-fold increased risk if topiramate is used during pregnancy. The study does, however, suggest that the prevalence of major congenital malformations may be greater than the approximately 4% described in the product information. The primary analysis from this study reports a prevalence of major congenital malformations of 6.29%. While the specific analysis, which may be more likely to capture cases with actual exposure to topiramate, reports a prevalence of 9.51%. These data, suggest that the topiramate product information should be updated to reflect these more recent data and the higher prevalence of major congenital malformations that have been observed following topiramate use during pregnancy.

Neurodevelopmental disorders

Whilst the available data relating to the risk of neurodevelopmental disorders remains relatively limited, some important new studies have become available since this was previously considered by the CHM. These are studies by Bjørk and colleagues (2022) and Dreier and colleagues (2023) in the Nordic registries and preliminary data from the study by

Hernandez-Diaz and colleagues (2022) examining data in US healthcare claims databases. These three studies add considerably to the body of evidence to inform our understanding of this risk. These studies along with the cohort study by Blotière and colleagues (2020) and the cross-sectional observational studies in the UK Epilepsy and Pregnancy Registry by Knight and colleagues (2020) and Bromley and others (2016) within the UK Epilepsy and Pregnancy Registry provide the more robust data in relation to this risk.

It is notable that these studies report conflicting findings with the studies by Dreier and colleagues, Bjørk and colleagues, and Knight and colleagues suggesting an increased risk of neurodevelopmental disorders such as intellectual disability, attention deficit hyperactivity disorder and autism spectrum disorder along with poorer adaptive behaviour. While the remaining studies do not support an increased risk of neurodevelopmental disorders, including pervasive developmental disorders and mental retardation, or detrimental effects on cognitive functioning.

The study designs, methodology and cohort sizes within these studies will have an impact on the robustness of their findings. There are some important differences between these studies, including the indications for use of topiramate, the doses used and the duration of follow-up, that may in part explain the differences observed.

The four largest studies (Bjørk and others 2022, Blotière and others 2020, Dreier and others 2023, and Hernandez-Diaz and others 2022) are cohort studies within population or healthcare databases that include large cohorts of topiramate exposed pregnancies and explore similar but not identical outcomes. In terms of outcomes, there is likely to be under recording of neurodevelopmental disorders in healthcare databases (Charlton 2017). In addition, using broad or specific definitions of outcomes based on inclusion/exclusion of specific ICD-10 codes could impact on the results. Hernandez-Diaz and colleagues used broader definitions, whereas Bjork and colleagues used a more outcome specific definition. There are also some other important differences between these studies that may in part explain the differences observed. In particular, the indications for use in the topiramate cohorts and the duration of follow-up in the studies.

The study by Blotière and colleagues appeared to include predominantly women who received topiramate for indications other than epilepsy compared with approximately 50% in the studies by Bjørk and colleagues and Hernandez -Diaz and colleagues. The findings of Bjørk and colleagues and Knight and colleagues suggest a dose-related risk, therefore it is possible that the study by Blotière and colleagues may have underestimated the risk as it is likely that the women in this study were exposed to lower doses of topiramate. Furthermore, the duration of follow-up in the study by Blotière and colleagues was shorter than that in the study by Bjørk and colleagues and hence this study may only have been able to capture the more severe disorders that are likely to be diagnosed earlier and again may have underestimated the risk.

With regards to the study by Hernandez-Diaz and colleagues, whilst this has the largest cohort of topiramate exposed pregnancies, at the time of the CHM consideration, the study had not been published and only preliminary results were available, which did not include full information on the methods and results. The cross-sectional studies (Knight and others 2020, Bromley and others 2016) enable smaller cohort sizes to be studied, however, they are only powered to detect large effect sizes and where an increased risk has been observed this is compared with a normative sample. Hence these studies cannot rule out more moderate effect sizes and may be subject to confounding due to baseline differences between the groups. Neither of these cross-sectional studies allow for definitive conclusions to be reached and the authors acknowledge the need for more studies.

The evidence for topiramate and the risk of neurodevelopmental disorders is not as clear or as consistent as that available for valproate, where the non-clinical and clinical data show good alignment. Nevertheless, taking into account the strengths and limitations of the available data, it is considered that the data support the possibility of an increased risk of neurodevelopmental disorders, including intellectual disability, autism spectrum disorder and attention deficit hyperactivity disorder, in children that are prenatally exposed to topiramate. Also, there are some data suggesting that the risk of autistic spectrum disorders and intellectual disability may be dose dependent.

Reproductive toxic effects on the fetus or neonate

Data from pregnancy registers (Hernandez Diaz and others 2017), population birth registers (Killic and others 2014, Veiby and others 2014) and the more recent study by Van Marter and colleagues (2021) in the multicentre Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study, suggest that prenatal exposure to topiramate monotherapy is associated with babies being born small for gestational age and/or at lower birthweights.

None of the studies that have been conducted to date have examined the long-term consequences of the risk of small for gestational age with topiramate, however, it is generally recognised that effects on fetal growth either assessed antenatally (intrauterine growth retardation) or at the time of birth are significantly associated with worse neurodevelopmental outcomes and this is true for both preterm and term-born children (Sacchi C and others 2020, Arcangeli T and others 2012).

The available data on the risk of fetal loss and preterm birth following topiramate use during pregnancy is very limited and no definitive conclusions can be reached on these risks based on the currently available data.

Conclusions

The accumulating data suggest that topiramate use during pregnancy is associated with the potential for significant harm to the unborn baby. The magnitude of the teratogenic risk associated with the use of topiramate during pregnancy does not appear to be as high as that seen with valproate and the nature of the risks not as severe. Also, the data on the risk of neurodevelopmental disorders with topiramate is more limited and currently it is unclear how it compares with that of valproate. However, when considering the risks seen with topiramate with that of other antiepileptic drugs/antiseizure medications (excluding valproate) the available data suggest that topiramate is amongst the antiepileptic drugs/antiseizure medications associated with a higher risk of congenital malformations, that it potentially has the highest risk of effects on fetal growth, and it may be associated with a potentially dose-dependent risk of neurodevelopmental disorders.

Given these risks it is essential that any decision to initiate topiramate in a patient who are able to get pregnant is made jointly by the patient and their healthcare professional and is fully informed by the harms to the unborn child associated with the use of topiramate during pregnancy and for patients with epilepsy also considers the risks associated with poorly managed epilepsy.

For the prophylaxis of migraine indication there are already contraindications for the use of topiramate in pregnancy and in women of childbearing potential not using effective contraception.

In clinical guidelines for the management of epilepsies, topiramate is not recommended as a first-line monotherapy treatment nor is it the only add-on treatment that is suitable for the management of specific types of seizures. Furthermore, there do not appear to be sub-populations with specific types of seizures that can only be adequately treated with topiramate. Given the availability of suitable alternatives, further restrictions to the use of topiramate in pregnancy and in women of childbearing potential would not necessarily deny access to the only suitable antiepileptic drug/antiseizure medication.

Overall, the significant harms to the unborn child that are associated with the use of topiramate during pregnancy coupled with the exposure data suggesting increasing use in female patients of childbearing age and high number of topiramate exposed pregnancies suggest that further restrictions to the use of topiramate in women of childbearing potential and in pregnancy are necessary. These restrictions should aim to reduce the number of exposed pregnancies and ensure that any decision to initiate topiramate in patients who can get pregnant is informed by both the benefits of treatment and the serious harms associated with its use during pregnancy.

6. CHM advice

The CHM considered the available non-clinical and clinical evidence on the safety of use of topiramate during pregnancy along with patients' perspectives on topiramate. The CHM was asked to advise on whether the new evidence changed the benefit-risk profile in any population or indication and whether the current risk minimisation measures were sufficient. If not, the CHM was asked to advise on which of a range of additional risk minimisation options were appropriate and proportionate.

Overall, the CHM advised that the use of topiramate during pregnancy is associated with significant harm to the unborn child and that the accumulating data suggest that:

- topiramate is amongst the antiepileptic drugs/antiseizure medications that are associated with a higher risk of congenital malformations (prevalence 4 to 9 per 100 babies).
- the risk of congenital malformation with topiramate appears to be dose-dependent, however, a threshold dose below which no risk exists cannot be established.
- when topiramate is used as part of a polytherapy regimen the risk of congenital malformations may be higher than with polytherapy regimens not including topiramate.
- topiramate is associated with a high prevalence of babies being born small for gestational age (~18 per 100 babies affected) that may be higher than that with some other antiepileptic drugs/antiseizure medications.
- topiramate may be associated with an approximately 2 to 3 times increased risk of intellectual disability, autistic spectrum disorders and attention deficit hyperactivity disorder.

The CHM also considered that the data from the Medicines and Pregnancy Registry and CPRD Aurum, raised concerns that the existing contraindications to use in pregnancy in migraine patients are not being adhered to and further measures are needed to reinforce awareness and improve adherence.

Considering the potential for significant harm to the unborn child associated with the use of topiramate during pregnancy, the CHM advised that there is a need to introduce further restrictions to the use of topiramate in girls and women who are able to get pregnant and in pregnancy. These measures would help to ensure that any decision to initiate topiramate in a girl or woman who is able to get pregnant should be based on an informed discussion

between the healthcare professional and the patient to ensure there is a clear awareness and understanding of the risks and the necessary precautions associated with its use.

Therefore, the CHM advised that the following further risk minimisation measures should be introduced for topiramate containing medicines:

- a) Use of topiramate should be contraindicated in patients who are able to get pregnant unless the conditions of a Pregnancy Prevention Programme (PPP) are fulfilled.
- b) For prevention of migraine indication, use of topiramate should continue to be contraindicated in pregnancy.
- c) Use of topiramate in epilepsy should be contraindicated in pregnancy unless there is no suitable other treatment.
- d) The PPP to be introduced for topiramate should include the following conditions:
 - Assessing the patient's individual circumstances including the potential for pregnancy for all patients and the ability to comply with the PPP;
 - Ensuring the patient is aware and understood:
 - the risks associated with use during pregnancy.
 - the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
 - the need to use effective contraception for the duration of treatment and for at least 4 weeks after the last dose of topiramate.
 - the need for regular (at least annual) review of treatment.
 - the actions that they need to take if they are thinking of planning a pregnancy or in case of pregnancy.
- e) Updates should be made to the product information to better reflect the currently available evidence on the nature and the magnitude of the risks of topiramate use during pregnancy, including the risk of neurodevelopmental disorders, effects on fetal growth, and risk of congenital malformations.
- f) Educational materials for patients and healthcare professionals (Patient Card, Patient Guide, Healthcare Professional Guide, Annual Risk Awareness Form) should be introduced and these be developed with the input of relevant stakeholders.

The CHM also noted the potential for an interaction between topiramate and systemic hormonal contraceptives, which may impact on the efficacy of some contraceptive methods. To help reduce the risk of topiramate exposed pregnancies, it was considered that the information available for patients and healthcare professionals needs to provide clear information about the potential impact of topiramate and the contraceptive methods that will be most suitable to use alongside topiramate.

The CHM also commented that the accumulating safety data along with exposure data suggesting increasing usage in women of childbearing age suggested it would be important to reconsider the place of topiramate in clinical guidance. In particular, for its use in the prophylaxis of migraine as this is a condition that is more prevalent in women than men and occurs more commonly in those of childbearing age.

The CHM also considered that to support successful implementation of the restrictions to the use of topiramate in women of childbearing potential and during pregnancy it will be important to involve patients and healthcare professionals in the implementation of the PPP, particularly the development of the risk minimisation materials. Therefore, the CHM advised that an expert working group should be established to advise on the implementation of the PPP.

7. Advice of the CHM Topiramate Implementation Expert Working Group

The CHM considered that to support successful implementation of the new risk minimisation measures in women of childbearing potential and during pregnancy would require a significant change in clinical practice, particularly in migraine which is usually managed in general practice. It was also recommended that it would be important to learn from the experience of introducing a PPP for valproate. The CHM also advised that it was essential to involve patient representatives and healthcare professionals in the development of the Educational Materials to accompany the PPP. Consequently, the CHM established the Topiramate Implementation Expert Working Group (TIEWG). The TIEWG included representatives from professional bodies and healthcare system bodies including NHS England (NHSE) and NICE.

The terms of reference were to advise the CHM on:

- plans for implementation in healthcare systems of the new advice of the CHM on topiramate,
- development of communication and educational materials to support and record informed prescribing decisions,
- plans for measurement of compliance with the recommendations,
- plans for the monitoring the effectiveness of risk minimisation measures and any future research.

The TIEWG met three times between June 2023 and March 2024.

The implementation group noted the CHM recommendations that the growing body of evidence relating to the harms to the unborn child associated with the use of topiramate in pregnancy coupled with the increasing usage in women of childbearing age, warranted strengthened risk minimisation measures. In particular, the implementation group noted that the introduction of a PPP and new contraindications to use were considered necessary to reduce the number of exposed pregnancies and help ensure informed decision making.

The implementation group discussed the impact on clinical practice that will result from the introduction of a PPP for topiramate, particularly in migraine which is a condition that affects around 30% of women at some point in their lives. It was recommended that given the current workforce and capacity within the NHS, the approach to implementation needs to:

- allow the diagnosis and ongoing treatment of migraine and epilepsy to continue to be managed in line with current clinical pathways and to ensure responsibility lies with the clinician who primarily prescribed topiramate (in general practice for migraine and secondary care for epilepsy),
- support the delivery of the PPP through a multidisciplinary team where allied healthcare professionals, such as specialist nurses and pharmacists, assist neurologists and GPs. Therefore, it is necessary to ensure these groups are also included in communication and education,
- provide appropriate flexibility for certain aspects of the PPP such as priority for and periodicity of review. Such as identifying priority groups for review and allowing less frequent reviews following agreement with the patient and based on their individual circumstances.

The input and views of the implementation group were sought on the Educational Materials to support the PPP (the Healthcare Professional Guide, the Annual Risk Awareness Form, the Patient Guide and the Patient Card) and it was commented that:

- the aim should be for the materials to be as concise as possible and avoid unnecessary repetition. In line with this it was recommended that separate versions of the Healthcare Professional and Patient Guides and Annual Risk Awareness Forms should be provided for the epilepsy and migraine patient populations.
- as topiramate may affect how well some hormonal contraceptive methods work the advice regarding effective contraception should be consistent with that of the Faculty of Sexual and Reproductive Health. Specifically, that patients who are able to get pregnant should preferably be using an independent form of contraception such as a copper intrauterine device (Cu-IUD) or levonorgestrel intrauterine system (LNG-IUS), or depot medroxyprogesterone acetate plus a barrier method.
- a digital version of the Annual Risk Awareness Form along with appropriate coding in software systems would help support more effective implementation.
- Easy Read versions of materials would be valuable given health literacy issues and comorbid learning difficulties.

The implementation group supported seeking the views of the Patient Charities and Organisations on the Patient Educational Materials (Guide, Card) and key messages for communications. It was commented that given the potential for off-label use of topiramate in idiopathic intracranial hypertension it would be important that [IJHUK](#) is made aware of the communications arising from the review.

The implementation group endorsed that in monitoring the impact of the new risk minimisation measures consideration should be given to 1) process indicators – the extent of implementation of the planned risk minimisation measures and their impact on knowledge and behaviour in the target audience, and 2) outcome indicators – an overall level of risk control achieved by the risk minimisation measures, i.e. safety outcomes. Process indicators to be explored include assessment of the compliance with the risk minimisation tools (e.g. the Annual Risk Awareness Form), indicators related to knowledge/understanding of the risks and pregnancy prevention measures, and prescribing trends to assess clinical actions. Proposed outcomes were low (near zero) pregnancy cases exposed to topiramate. It was highlighted that a digitalised Annual Risk Awareness Form, which could be linked to other data sources, would help enable efficient monitoring of process indicators across the healthcare system.

The implementation group agreed that the aim should be for no exposed pregnancies for any indication other than epilepsy, where it is acknowledged that there may be a few women for whom topiramate might be the most effective and/or best tolerated medicine. The importance of unintended consequences, such as increased morbidity and mortality, was also raised. The possibility of an increase in GP referrals of women, in the target population, to secondary care was another important area that should be monitored where possible.

The England Medicines and Pregnancy registry and CPRD were agreed as important data sources to use to monitor the impact. However, it was agreed it would be important to explore what other data sources exist in Scotland, Wales and Northern Ireland that might provide an opportunity to collect and analyse data on the impact of the new risk minimisation measures for topiramate.

8. Next steps

The MHRA has issued a Drug Safety Update to inform healthcare professionals of the new safety measures. We have also engaged with relevant professional and healthcare bodies, to inform them of these new measures and to ask them to take the necessary action to implement them.

The updates are being implemented in the product information for topiramate containing products.

Educational materials (Patient Card, Patient Guides, Healthcare Professional Guides and Annual Risk Awareness Forms) are also available to support discussions between patients and prescribers about the risk of taking topiramate during pregnancy and the steps needed to avoid becoming pregnant while taking this medicine.

The MHRA will monitor the impact of these new measures and seek advice from the CHM and other invited experts as needed.

If you are a patient on topiramate please discuss any concerns you have with your healthcare professional.

Patients taking topiramate for epilepsy should not stop topiramate without advice from their healthcare professional. A healthcare professional will advise on other suitable treatments and how to switch medication safely.

Any patient who thinks they are or might be pregnant should contact their doctor immediately.

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10. Glossary of terms

Antiepileptic drug

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

Antiseizure medication

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.

Attention deficit hyperactivity disorder (ADHD)

ADHD is a mental health condition that is defined through analysis of behaviour. People with ADHD show a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with day-to-day functioning and/or development.

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.

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.

Clinical Practice Research Datalink Aurum

The CPRD primary care database contains anonymised computerised longitudinal records of patients registered with contributing primary care practices across the UK. CPRD contains patient registration information, and all care events that general practice staff record. This includes demographic information, medical diagnoses, and prescriptions issued in primary care. CPRD Aurum consists of data from practices that use the EMIS GP software.

Cognitive abilities

Intellectual or thinking skills.

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.

Comorbidity/Comorbidities

Comorbidity means more than one disease or condition is present in the same person at the same time. Conditions described as comorbidities are often chronic or long-term conditions.

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.

Control group

The control group is defined as the group in an experiment or study that does not receive the substance, drug, treatment that is being tested and is used by the researchers as a benchmark to measure how the other tested subjects do.

Cross sectional observational study

A study that involves looking at data from a population at one specific point in time. This type of study can be used to describe the characteristics that exist in a population and gather preliminary data to support further research but cannot be used to determine cause and effect.

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.

Efficacy

In medicine, efficacy refers to the ability of a medicinal product or a treatment to provide a beneficial effect. Such as the ability of antiepileptic drugs/antiseizure medications to prevent or reduce the frequency of seizures in people with epilepsy.

Embryofetal toxicity

The adverse effects on the developing fetus that can result from exposure to chemical or physical agents prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity.

Epidemiological studies

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

Epilepsy

A brain condition characterised by fits or seizures.

Fetal growth restriction

Fetal growth restriction is a condition where a baby is smaller than expected or when a baby's growth slows or stops during pregnancy. It is also called intrauterine growth restriction.

Fetus

An unborn baby developing in the mother's womb.

Focal seizures

When an epileptic seizure starts in one side of the brain it's called a focal onset seizure or a focal seizure; both terms mean the same thing. Until recently these seizures were called partial seizures. When person has no loss of awareness of their surroundings during it, it is called a focal onset aware seizure. This type of seizure used to be called a simple partial seizure. When the person's awareness of what is happening around them is affected at any time during the seizure, it's called a focal impaired awareness seizure. This type of seizure used to be called a complex partial seizure.

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.

Gestational age

Gestational age is the common term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the woman's last menstrual cycle (period) to the current date. A normal pregnancy can range from 38 to 42 weeks.

Good Laboratory Practice

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

Hazard ratio (HR)

Hazard ratio (HR) is a measure of an effect of an intervention on an outcome of interest over time. Hazard ratio is reported most commonly in time-to-event analysis or survival analysis (i.e. when we are interested in knowing how long it takes for a particular event/outcome to occur). A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and value less than 1 suggests a decreased risk. An adjusted hazard ratio is a measure of the effect that has taken into account other factors that may affect the relationship.

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.

Human therapeutic dose

The dose of drug required to generate the desired therapeutic effect in humans.

Hypospadias

A birth defect in boys where the opening of the urethra (the tube that carries urine from the bladder to the outside of the body) is not located at the tip of the penis.

ICD-10

The International Classification of Diseases, Tenth Revision (ICD-10) is a system used by physicians to classify and code all diagnoses, symptoms and procedures.

Incidence/Incidence rate

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.

Intellectual disability

Intellectual disability is when a child has major difficulty or delay in acquiring skills across most developmental areas including motor (movement) skills, communication and speech, social interaction, and play and learning (cognitive skills). There are different degrees of intellectual disability, ranging from mild to profound.

Intelligence Quotient (IQ)

A total score derived from a set of standardized tests or subtests designed to assess human intelligence.

Intrauterine growth retardation/restriction

A condition where a baby is smaller than expected or when a baby's growth slows or stops during pregnancy.

In utero

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

Lennox-Gastaut syndrome

This syndrome usually begins between the ages of 3 and 5 but can start as late as adolescence. Children may have several different types of seizure with this syndrome. These include tonic (where the muscles suddenly become stiff), atonic (where the muscles suddenly relax), myoclonic, tonic clonic and atypical absences. Many children also develop learning difficulties as well as behaviour problems.

Low birth weight

This term is used if a baby is born after 37 weeks and weighs less than 2.5kg (5.5 lb) when they're born. Around seven in 100 babies born in the UK have a low birth weight.

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.

Median

The median is an average that is found by listing the values in order and finding the middle value.

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 function/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.

National Birth Register

These are population-based registers that collect data from medical records about the prenatal, delivery and neonatal care of pregnant women and their offspring. Such registers support the monitoring of the health of pregnant women and their offspring and are used for research purposes.

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.

Neurodegenerative/Neurodegeneration

Gradual loss of structure or function of nerve cells in the brain (neurons), including death of the nerve cells. Neurodegenerative diseases can influence many functions including an individual's movement, speech, memory, intelligence and more.

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.

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.

Odds ratio (OR)

A measure of risk (effect) for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk. An adjusted odds ratio is a measure of the effect that has taken into account other factors that may affect the relationship.

Partial seizures

See focal seizures

Patient Information Leaflet

Medicine packs 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.

Polytherapy

The use of two or more medicines or therapies to treat a disease, symptom or condition.

Postnatal

Relating to or denoting the period after childbirth.

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.

Preterm birth

Preterm birth, also known as premature birth, is the birth of a baby at fewer than 37 weeks' gestational age, as opposed to the usual of about 40 weeks.

Prevalence

The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Prospective 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.

p-value (p)

A measure of the statistical probability of an event occurring by chance. A smaller p-value suggests the event is less likely to be due to chance; a larger p-value suggests the event is more likely to have occurred by random chance.

Regulatory compliant study

A study that is conducted in line with the rules and standards that are defined by a regulatory authority, such as the Medicines and Healthcare products Regulatory Agency.

Reproductive toxicity

The occurrence of adverse effects on the male or female reproductive system that may result from exposure to chemical or physical agents.

Residual confounding

Residual confounding occurs when a risk factor has not been adequately adjusted for in the statistical analysis. The consequence is that the estimated association is not the same as the true effect.

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 (RR)

A risk ratio (RR), also called relative risk, is a measure of effect and compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk. An adjusted risk ratio/relative risk is a measure of the effect that has taken into account other factors that may affect the relationship.

Seizure

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

Sensitivity analysis/analyses

Sensitivity analysis is a way to test how changing one or more factors in a model affects the outcome.

Small for gestational age

Small for gestational age is a term used to describe babies that are smaller than usual for the number of weeks of pregnancy.

Spontaneous abortion

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

Standard deviation (SD)

A measure of the amount of variation of a set of values. A low standard deviation indicates that the values tend to be close to the mean (the average) of the set, while a high standard deviation indicates that the values are spread out over a wider range.

Statistical analysis

Statistical analysis is the collection and interpretation of data in order to uncover patterns and trends.

Statistical significance

A statistical interpretation of data that indicates that a result is unlikely to have occurred by chance.

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>

Teratogen/Teratogenic

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

Tertiary care

Tertiary care is highly specialised medical care provided to patients with complex, severe or rare health conditions. Patients usually access tertiary care after being referred by primary or secondary care providers.

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.

Trimester

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

US Medicaid

The Medicaid Program provides medical benefits to groups of low-income people, some who may have no medical insurance or inadequate medical insurance.

VABS – Vineland Adaptive Behavior Scales

A standardised tool that is used to support the diagnosis of intellectual and developmental disorders, autism, and developmental delays. The areas of assessment include communication, activities of daily living, social relationships and development. A normative sample is a subgroup within a population that is used to assess what is normal for that population.