

**From the Chief Medical Officer
Dr Michael McBride**



Department of
Health

An Roinn Sláinte

Mánnystrie O Poustie

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HSS(MD) 14/2021

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Castle Buildings

Stormont Estate

BELFAST

BT4 3SQ

Tel: 028 9052 0563

Email: Michael.McBride@health-ni.gov.uk

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Dear Colleague

**SAFETY OF ANTIEPILEPTIC DRUGS IN PREGNANCY: UPDATED ADVICE
FOLLOWING COMPREHENSIVE SAFETY REVIEW**

Actions for prescribers¹

- At initiation and as part of the recommended annual review for patients with epilepsy, specialists should discuss with women the risks associated with antiepileptic drugs and with untreated epilepsy during pregnancy and review their treatment according to their clinical condition and circumstances. The MHRA have produced a [safety information leaflet⁶](#) developed following consultation with relevant stakeholder organisations, charities, and patient groups to assist with this discussion
- Urgently refer women who are planning to become pregnant for specialist advice on their antiepileptic treatment
- All women using antiepileptic drugs who are planning to become pregnant should be offered 5mg per day of folic acid before any possibility of pregnancy
- For lamotrigine, levetiracetam or any antiepileptic drugs that can be used during pregnancy, it is recommended to
 - use monotherapy whenever possible
 - use the lowest effective dose
 - report any suspected adverse effects experienced by the mother or baby to the [Yellow Card scheme⁷](#)

The Health and Social Care Board is asked to work with the Business Services Organisation to monitor the impact of this updated guidance¹ through examination of prescribing and dispensing data, focussing on trends in use of antiepileptic drugs in women of childbearing potential.

Overview

A review of the risks of major congenital malformations and of adverse neurodevelopmental outcomes for antiepileptic drugs by the Commission on Human Medicines (CHM) has confirmed that lamotrigine (Lamictal) and levetiracetam (Keppra) are the safer of the medicines reviewed during pregnancy.¹ This review was initiated in the context of the known harms of valproate in pregnancy.² Clinicians should use the information detailed in the review when discussing treatment options with women in the treatment of epilepsy, at initiation, at routine recommended annual reviews and with women who are planning to become pregnant.

Much of the evidence base in the CHM review relates to epilepsy, however it is important to consider this information when commencing or reviewing anti-epileptic medication that are prescribed for conditions other than epilepsy (for example pain, or anxiety) in women of childbearing potential. The most updated advice will be available in the product information and should be consulted for these medicines when necessary.¹

It is important that everyone affected by the updated information is made aware as soon as possible.

Background

Antiepileptic drugs are crucial to control seizures and other epilepsy symptoms and untreated epilepsy can cause harm to both the mother and the unborn baby. However, use of these antiepileptic drugs during pregnancy has been associated with a range of harmful effects to the baby.

In particular, valproate (Epilim) is highly teratogenic and evidence supports a rate of congenital malformations of 10% in infants whose mothers took valproate during pregnancy and neurodevelopmental disorders in approximately 30% to 40% of children. For this reason, valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated, as judged by an experienced specialist, it is contraindicated unless a [pregnancy prevention programme](#) is in place.²

Our earlier correspondence outlined actions to be taken by all relevant health care professionals (Circular HSS(MD) [8/2018](#) and [27/2018](#))^{3,4} and updated [educational materials to support healthcare professionals and female patients on valproate](#) were re-circulated to UK healthcare professionals by Sanofi in December 2020.

We remind all healthcare professionals that they must continue to identify and review all female patients on valproate, including when it is used outside the licensed indications, and provide them with the patient information materials every time they attend their appointments or receive their medicines (including the patient information leaflet at dispensing) to ensure that the conditions of the valproate pregnancy prevention programme² are met, as described in the documents.

National review of safety data

In the context of the known harms with valproate, the CHM has reviewed available safety data relating to the use of other key antiepileptic drugs in pregnancy for the risk of major congenital malformations, neurodevelopmental disorders and delay, and other effects on the baby. The key antiepileptic drugs were selected for the review on the basis of their place in UK clinical practice.¹

On this basis, data on the use of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide in pregnancy were reviewed. The data and conclusions from a European review in 2018 of levetiracetam in which the UK participated were also taken into account.¹

Full information on the antiepileptic drugs included in the review, in addition to studies considered and findings from these studies, can be found in the [public assessment report](#).⁵ This report also includes a plain language summary of the review and findings.

Summary of key conclusions of review

- Lamotrigine – Studies involving more than 12,000 pregnancies exposed to lamotrigine monotherapy consistently show that lamotrigine at maintenance doses is not associated with an increased risk of major congenital malformations
- Levetiracetam – Studies involving more than 1,800 pregnancies exposed to levetiracetam do not suggest an increased risk of major congenital malformations
- For both lamotrigine and levetiracetam, the data on neurodevelopmental outcomes are more limited than those for congenital malformations. The available studies do not suggest an increased risk of neurodevelopmental disorders or delay associated with in-utero exposure to either lamotrigine or levetiracetam; however, the data is inadequate to rule out definitively the possibility of an increased risk
- For the other key antiepileptic drugs, data show:
 - an increased risk of major congenital malformations associated with carbamazepine, phenobarbital, phenytoin, and topiramate use during pregnancy
 - the possibility of adverse effects on neurodevelopment of children exposed in utero to phenobarbital and phenytoin
 - an increased risk of fetal growth restriction associated with phenobarbital, topiramate, and zonisamide use during pregnancy

It is also important to note, that some medicines included in the CHM review are also authorised for medical conditions other than epilepsy (for example, pain and anxiety). Much of the evidence base in the CHM review relates to epilepsy and, as such, focused on the risks and decisions for epilepsy treatment.

However, the advice in the product information should be considered to be relevant when prescribing these medicines for any indication to this patient group.¹

How to use the review findings

We are communicating the conclusions of this review to help support decisions by prescribers and women who are starting or currently being treated with antiepileptic medicines. This information should also be considered when selecting a medicine for girls with epilepsy who may need treatment into adulthood and in particular for women planning a pregnancy.⁸

Where new information has been identified or where it is considered that the product information (Summary of Product Characteristics, (SmPC), and patient information leaflet) could be more informative, the MHRA will also update these to reflect the latest information. The MHRA are working with relevant patient groups to ensure that the information to patients in the leaflets for each medicine is as clear as possible.

As outlined above, some medicines included in the review are also prescribed for medical conditions other than epilepsy (for example, pain and anxiety). When considering initiating any of these medications for any indication (including use off license), it is important that the advice in the product information is considered and discussed with the patient where necessary.¹

Additional information

It is important that everyone affected by the updated information is made aware as soon as possible. NICE are taking steps to review their guidelines where these medicines are recommended, including the assessment and management of bipolar disorder, depression in adults and antenatal and postnatal mental health to reflect this important advice.⁸

In summary, we acknowledge your commitment to the ongoing monitoring in this key patient safety area and the work undertaken to date in primary and secondary care to review patients and reduce the number of women of childbearing age taking valproate in Northern Ireland. It remains vital that all necessary steps are taken to ensure that all females of childbearing age who are taking medicines associated with an increased risk of congenital abnormalities have their treatment reviewed, are made aware of the risks and are offered effective pregnancy prevention advice and treatment or alternative medication, where clinically appropriate.

Yours sincerely



DR MICHAEL MCBRIDE
Chief Medical Officer



MRS CATHY HARRISON
Chief Pharmaceutical Officer

1. MHRA 2021. Drug Safety Update. Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review. Available at: <https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review>
2. MHRA 2018. Guidance. Valproate use by women and girls. Available at: <https://www.gov.uk/guidance/valproate-use-by-women-and-girls>
3. Department of Health NI October 2018. Circular HSS(MD) 27/2018. Available at: https://www.health-ni.gov.uk/sites/default/files/publications/health/hss-md-27-2018_0.pdf
4. Department of Health NI April 2018. Circular HSS(MD) 8/2018. Available at: <https://www.health-ni.gov.uk/sites/default/files/publications/health/hss-md-08-2018.pdf>
5. MHRA 2021. Public Assessment Report <https://www.gov.uk/government/publications/public-assessment-report-of-antiepileptic-drugs-review-of-safety-of-use-during-pregnancy>
6. MHRA 2021. Epilepsy medicines and pregnancy. Patient leaflet <https://www.gov.uk/government/publications/epilepsy-medicines-and-pregnancy>
7. MHRA 2021 Yellow Card Scheme. Available at <https://yellowcard.mhra.gov.uk/>
8. MHRA 2021. News release <https://www.gov.uk/government/news/safety-review-of-epilepsy-medicines-in-pregnancy-women-who-may-become-pregnant-urged-to-discuss-treatment-options-with-their-doctor>

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