Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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In our first article, in view of data showing ongoing exposure to valproate in pregnancy, we remind healthcare professionals of the risks in pregnancy and the current Pregnancy Prevention Programme requirements, and provide information about the potential risks of valproate in other patients following a review of the latest safety data. Following advice from the Commission on Human Medicines (CHM), new safety measures for valproate-containing medicines are to be put in place in the coming months. Information is provided on page 2.

Next, on page 5 we summarise recent advice relating to COVID-19 vaccines and medicines published since the November 2022 issue of Drug Safety Update up to 8 December 2022. And on page 6, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines.

If you have been forwarded this issue of Drug Safety Update, subscribe directly via our website.

We also remind all healthcare professionals that the public consultation on how the MHRA communicates medicines and medical devices safety information is open.

Valproate: reminder of current Pregnancy Prevention Programme requirements; information on new safety measures to be introduced in the coming months

In view of data showing ongoing exposure to valproate in pregnancy, this article reminds healthcare professionals of the risks in pregnancy and the current Pregnancy Prevention Programme requirements, and provides information about the potential risks of valproate in other patients following a review of the latest safety data. Following advice from the Commission on Human Medicines (CHM), new safety measures for valproate-containing medicines are to be put in place in the coming months.

The CHM has established an implementation group with a cross-health sector membership to support the safe introduction of the new measures into clinical practice. This will be via a phased programme currently under development according to patient safety priorities, and developed in collaboration with the healthcare bodies, to ensure ongoing patient care is not disrupted. No action is currently needed from patients.

Patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so. Any patient who thinks they are pregnant while on valproate should be advised to talk to a specialist urgently.

Before initiating valproate in patients younger than 55 years, healthcare professionals should consider all other suitable therapeutic options and consult the findings of the epilepsy medicines in pregnancy review.

Advice for healthcare professionals:

- continue to follow the existing strict precautions, including that valproate should not be prescribed to female children or women of childbearing potential unless other treatments are ineffective or not tolerated and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme
- following a new safety review conducted in light of concerns that the current regulatory requirements for safe use are not being consistently followed, the Commission on Human Medicines (CHM) has advised that there should be greater scrutiny of the way valproate is prescribed and that further risk minimisation measures are required – in particular that 2 specialists should independently consider and document that there is no other effective or tolerated treatment for patients aged under 55 years
- consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55 years
- these new measures will be implemented over the coming months. In the meantime, GPs and pharmacists should continue to provide repeat prescriptions for valproate and dispensers should continue to ensure patients receive the patient card, a copy of the Patient Information Leaflet and packaging bearing pregnancy warnings
- **patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so**

Current safety measures for valproate due to risks with pregnancy exposure

Valproate (as sodium valproate or valproic acid) is authorised for use in epilepsy and bipolar disorder. It is also used outside of the licence (‘off label’) to treat other conditions.

Valproate has a high teratogenic potential. Exposure of an unborn child to valproate in utero is associated with a high risk of congenital malformations (11%) and neurodevelopmental disorders (30–40%), which may lead to permanent disability. The available evidence does not support a specific at-risk gestational period and the possibility of a risk of valproate throughout pregnancy cannot be excluded.

Due to the serious harms to an unborn baby associated with use of valproate in pregnancy, the existing advice is that valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. As a further strengthening of this position in April 2018, we introduced the Valproate Pregnancy Prevention Programme (PPP) as a requirement of any valproate use in patients of childbearing potential. We continue to closely monitor the impact of these requirements.

Safety review of data relating to valproate

In 2022, the Commission on Human Medicines (CHM) considered a review of safety data relating to valproate. This review included prescribing data showing continued use of valproate in female patients and also some use during pregnancy, as well as evolving information about potential risks in male patients. The CHM also considered the views of patients and other stakeholders on the current use of valproate and on how the risks of valproate are currently managed.

Although rates of valproate usage in female patients have declined since the introduction of the Pregnancy Prevention Programme in 2018, recently there has been a plateauing of this decline and there is no room for complacency (shown in the March 2022 report of the Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England). Furthermore, although the number of pregnant women prescribed valproate in a 6-month period has fallen since 2018, the latest report of the registry, published September 2022, noted that 17 female patients prescribed valproate in a month in which they were pregnant were identified as new additions to the registry between October 2021 and March 2022.

The review also considered data for other potential risks, including that, as indicated in the current product information, valproate may impair male fertility, and there is some evidence that this is reversible upon discontinuation. In addition, data were considered from studies in juvenile rats and adult rats and dogs reporting adverse effects to the male reproductive system in animals receiving valproate, as well as non-clinical studies on the potential for epigenetic effects of valproate and transgenerational risks. There are currently limited data available on these risks in humans and further studies are planned. There is also an ongoing retrospective study on the outcomes of babies exposed to valproate via paternal use.

CHM advice and recommended new measures

On the basis of the evidence, the CHM has recommended a number of regulatory actions to further strengthen safety measures for valproate. These measures will be introduced over the coming months according to patient priorities so they can be introduced safely. Advice on the timing of introduction will be provided once the CHM's implementation group has finalised plans and after full engagement with stakeholders. No action is needed at present except for women of childbearing potential not on the Pregnancy Prevention Programme.

The CHM recommends that no patients (male or female) under the age of 55 years should be initiated on valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment. For patients under 55 years currently receiving valproate, 2 specialists should independently consider and document that there is no other effective or tolerated treatment or the risks do not apply. The CHM has advised that these measures should apply to people under the age of 55 because this is the age group most likely to be affected by the risks of valproate when taken during pregnancy and the possible risk of impaired fertility in males.

Other measures recommended by CHM included further warnings in the product information, improved educational materials, and better monitoring of healthcare professionals' compliance with the new measures.

Clinicians should continue to consult the findings of the epilepsy medicines in pregnancy review when considering prescribing of epilepsy medicines in female patients, particularly that lamotrigine (Lamictal) and levetiracetam (Keppra) were not associated with an increased risk of birth defects compared with the rate in the general population. We also note that the risks associated with topiramate use in pregnancy are under review.

Adherence to Pregnancy Prevention Programme requirements must continue

Full adherence to the Valproate Pregnancy Prevention Programme must continue. This includes the need for annual review and a signed Acknowledgement of Risk Form. All patients who think they are pregnant while on valproate should be advised to talk to a specialist urgently. Patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so.

Use of valproate outside of the licenced indications

We are aware valproate is used outside of the licenced indications to treat conditions such as migraine and other mental health conditions. Prescribers should consider the risks associated with valproate and note that use of valproate outside of the licence may carry greater prescriber responsibilities than when used within the terms of its licence (see GMC guidance for unlicensed medicines). Valproate must be prescribed and dispensed to women of childbearing potential according to the Valproate Pregnancy Prevention Programme.

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COVID-19 vaccines and medicines: updates for December 2022

Summaries of Yellow Card reporting

We continue to publish the summaries of the Yellow Card reporting for the COVID-19 vaccines being used in the UK. The report summarises information received via the Yellow Card scheme and includes other data such as usage of COVID-19 vaccines and relevant epidemiological data. The report is updated regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

The MHRA will be updating the format of the summary of Yellow Card reporting in future publications to focus on the coronavirus vaccines being administered as part of the autumn booster campaign. Information on monovalent vaccines used in the previous primary and initial booster campaign will remain available as a record on the government website.

Other recent MHRA updates on coronavirus vaccines and medicines:

We have also recently:

- authorised the Pfizer/BioNTech COVID-19 vaccine for use in infants and children aged 6 months to 4 years after finding it meets the MHRA's acceptable standards of safety, quality and effectiveness

See guidance on COVID-19 for all our latest information, including after publication of this article. We previously included summaries of latest COVID-19 information in the September 2022, October 2022 and November 2022 issues of Drug Safety Update.

Reporting Yellow Cards

Report suspected side effects to medicines, vaccines and medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using:

- the dedicated Coronavirus Yellow Card reporting site
- the Yellow Card app (download from the Apple App store or Google Play store)

For products under additional monitoring (▼) such as the COVID-19 vaccines, you should report all suspected adverse side effects. This will allow the MHRA to identify new safety information for these products.

When reporting please provide as much information as possible, including information about medical history, any concomitant medications, onset timing, and treatment dates, and for vaccines, the product brand name and batch number.

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected side effects.

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Letters and medicine recalls sent to healthcare professionals in November 2022

Letters

In November 2022, the following letters were sent or provided to relevant healthcare professionals:

- Imbruvica (ibrutinib): New risk minimisation measures, including dose modification recommendations, due to the increased risk for serious cardiac events
- Stemetil (Prochlorperazine mesilate) 5 mg / 5 ml Syrup: permanent discontinuation due to laboratory test results demonstrating excess levels of N-nitrosomethylphenylamine
- Vincristine sulfate 1 mg/1 ml solution for injection (PL 04515/0008) – 2 mg in 2 ml Temporary supply of US stock of Vincristine sulfate Injection, USP 2 mg/2 ml (batch number GD0903AA) to mitigate supply disruption
- NovoRapid Penfill 100 units/ml solution for injection in cartridge (insulin aspart): supply of Stock with old Patient Information Leaflet to mitigate supply disruption in November 2022

Medicine Recalls and Notifications

In November 2022, recalls and notifications for medicines were issued on:

National Patient Safety Alert: Class 4 Medicines Defect Information: Prenoxad 1mg/ml Solution for Injection, Macarthys Laboratories (Aurum Pharmaceuticals Ltd/Ethypharm Group), due to potential missing needles in sealed kits, NatPSA/2022/009/MHRA. Issued 10 November 2022. Macarthys Laboratories (trading as Martindale Pharma, an Ethypharm Group Company), has notified the MHRA of a limited number of Prenoxad packs in a batch marketed in France with missing needles. Healthcare professionals and service providers should note the actions set out the alert before supplying Prenoxad kits.

Class 4 Medicines Defect Information: Macarthys Laboratories t/a Martindale Pharma, Venlafaxine XL 300 mg prolonged-release tablets, EL(22)A/47. Issued 16 November 2022. Martindale Pharma has made the MHRA aware that the GTIN in the 2D barcode and the printed variable data represents the branded version of the product (Venlalic XL 300 mg prolonged-release tablets). Healthcare professionals are advised to exercise caution when dispensing the products. Additional precautions should be considered by wholesalers and pharmacies using automated inventory systems to dispense the affected batch within the pharmacy or wholesale facility.

Class 4 Medicines Defect Information: Morningside Healthcare Limited, Hyoscine Butylbromide 20 mg Film-coated Tablets, EL (22)A/48. Issued on 21 November 2022. Morningside Healthcare Limited has informed the MHRA of an error with the Patient Information Leaflet (PIL) packaged in batch 22237001 of Hyoscine Butylbromide 20 mg Film-coated Tablets. Healthcare professionals are advised to exercise caution when dispensing the above batch and to check the PIL. If the pack contains the wrong PIL, remove and destroy it and provide a copy of the correct PIL.

Class 4 Medicines Defect Information: Lucis Pharma Ltd, Oxycodone Hydrochloride 10mg/ml oral solution, EL (22)A/49. Issued 29 November 2022. Lucis Pharma Ltd has informed the MHRA that there is a typographical error with text on the rear side of the outer packaging for Oxycodone Hydrochloride 10mg/ml Oral Solution. Healthcare professionals should exercise caution when dispensing or supplying this product. Please refer to the correct information stated on the bottle label and in the Patient Information Leaflet inserted in the pack.

The public consultation on how the MHRA communicates medicines and medical devices safety information to healthcare professionals is now open. The consultation is a unique opportunity to influence future MHRA safety communications and safety reporting systems so please encourage all healthcare professionals to complete the survey.

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