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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First, we advise that domperidone is no longer licensed for use in children younger than 12 years or those weighing less than 35 kg. This follows an absence of data for benefit, including findings from a placebo-controlled study in children with acute gastroenteritis that did not show domperidone to be more effective than placebo at relieving nausea and vomiting. We also remind healthcare professionals of contraindications and recommendations for dose and treatment duration in adults and adolescents introduced in 2014 (see page 2).

In our second article we advise you of the latest letters and alerts issued to healthcare professionals, including a further recall for ranitidine tablets from pharmacies and retail stores as a precautionary measure due to possible contamination with an impurity N-nitrosodimethylamine (NDMA), which has genotoxic and carcinogenic potential (page 4).

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Domperidone for nausea and vomiting: lack of efficacy in children; reminder of contraindications in adults and adolescents

Domperidone is no longer licensed for use in children younger than 12 or those weighing less than 35 kg. Results from a placebo-controlled study in children younger than 12 years with acute gastroenteritis did not show any difference in efficacy at relieving nausea and vomiting compared with placebo.

Advice for healthcare professionals:

Change of indication

- domperidone is now authorised for the relief of symptoms of nausea and vomiting only in adults and adolescents 12 years of age or older and weighing 35 kg or more
- consider alternative treatments to domperidone in children younger than 12 years of age who need relief of symptoms of nausea and vomiting

Reminder of contraindications

- European regulatory studies show that some physicians, including in the UK, are not aware of the important precautions for use of domperidone introduced in 2014
- domperidone is contraindicated:
    - in patients with moderate to severe hepatic impairment
    - in patients with known existing prolongation of cardiac conduction intervals (particularly QTc)
    - in patients with underlying cardiac diseases such as congestive heart failure,
    - in patients with significant electrolyte disturbances,
    - during co-administration with QT-prolonging drugs (for more information about considerations with apomorphine (see Drug Safety Update published April 2016)
    - during co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects)
    - in patients with hypersensitivity to domperidone
    - in patients with a prolactin-releasing pituitary tumour
    - in patients in which stimulation of the gastric motility could be harmful (for example, in patients with gastro-intestinal haemorrhage, mechanical obstruction, or perforation)

Reminder of recommendations for dose and treatment duration

- for adults and adolescents 12 years of age or older and weighing 35 kg or more, the recommended maximum dose in 24 hours is 30 mg (dose interval: 10 mg up to 3 times a day)
- domperidone should be used at the lowest effective dose for the shortest possible duration and maximum treatment duration should not usually exceed 1 week
- report suspected adverse drug reactions associated with domperidone to the Yellow Card Scheme

Lack of efficacy in the paediatric population younger than 12 years

Domperidone is a dopamine antagonist with antiemetic properties. A European review of the safety of domperidone in 2014 introduced new restrictions following continued reports of cardiac side effects (see later section). At the time, there were limited data to support paediatric use in the relief of the symptoms of nausea and vomiting, and studies were requested to provide further data to support efficacy.

A multicentre, double-blind, randomised, placebo-controlled, parallel-group, prospective study[1] evaluated the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged between 6 months and 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), patients were randomised to receive domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone per day), or placebo, 3 times a day, for up to 7 days. This study did not show domperidone suspension plus ORT to be significantly more effective than placebo plus ORT at reducing vomiting episodes during the first 48 hours after the first treatment administration.[1] The study did not reveal any new safety concern.

1. Leitz G, et al. J Pediatr Gastroenterol Nutr 2019; 69: 425–30.

A European review assessed this new evidence that domperidone is not as effective in this population as previously considered. Consequently, the product information for UK domperidone medicines has been updated to remove the indication in children **younger than** 12 years of age.

Domperidone is also used outside of its authorised indications in children in the UK for gastrokinetic effects in conditions other than nausea and vomiting. If a specialist physician considers, based on their professional judgement and available evidence of the medical condition, that domperidone use in any condition is justified in a child younger than 12 years, the patient or parent/caregiver should be fully informed of the potential benefits and risks of the different options (please see previous guidance on off-label use in Drug Safety Update, April 2009).

Reminder on the safe use of domperidone in accordance with the product information

The European safety review in 2014 confirmed risk of serious cardiac adverse drug reactions related to domperidone, including QTc prolongation, torsade de pointes, serious ventricular arrhythmia, and sudden cardiac death. The review concluded that additional risk minimising measures were necessary to improve the balance between benefits and risks and to reduce the risk of serious cardiac adverse events. More about these important restrictions, contraindications, and precautions can be found in the Drug Safety Update, December 2014.

Recent regulatory studies in several European countries, including the UK, show a proportion of physicians are not aware of the changes in indication and the contraindications introduced in 2014. All healthcare professionals are thus reminded to follow the precautions for safe use of domperidone-containing products (see list of contraindications on page 2).

Current usage of domperidone in the UK

Both tablet and oral suspension domperidone products are currently marketed in the UK. Data from the Clinical Practice Research Datalink (CPRD) suggest use of domperidone in the UK has reduced since 2014. Based on extrapolation from CPRD data, an estimated 5700–7500 children aged 0–11-years were prescribed domperidone in the UK in 2018 for any indication.[2]

2. The information presented here is based in part on data from the Clinical Practice Research Datalink however, the interpretation and conclusions regarding usage contained in this report are that of MHRA alone.

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Letters and drug alerts sent to healthcare professionals in November 2019

Letters sent in November 2019

- Lucentis (ranibizumab) 10 mg/ml pre-filled syringe: Update on plunger on syringe too stiff – see letter from September 2019 for previous advice

- Emerade 150, 300, 500 micrograms adrenaline auto-injectors: recall of all unexpired batches

Ranitidine – further recall

Previously we highlighted recalls for ranitidine medicines due to possible contamination with an impurity N-nitrosodimethylamine (NDMA), which has genotoxic and carcinogenic potential. Since publication of this article on 21 November 2019, a further recall alert has been issued:

Class 2 Medicines recall: Ranitidine 150mg Film-Coated Tablets, PL 20075/0063, Ranitidine 300mg Film-Coated Tablets, PL 20075/0064 (EL(19)A/40). Issued 5 December 2019. Accord Healthcare are recalling all unexpired stock from pharmacies and retail stores.
For the latest recalls, see Alerts and recalls for drugs and medical devices.

Other recall alerts

Class 2 Medicines recall for Emerade 150, 300 and 500 microgram solution for injection in a pre-filled syringe (MDR 57-08/19). Issued 28 November 2019. Pharmaswiss Česka republika s.r.o. (an affiliate of Bausch & Lomb UK Limited) is recalling all unexpired batches of Emerede Adrenaline Autoinjectors after identifying an error than can cause some pens to fail to activate.

Class 2 Medicines Recall: M&A Pharmachem Limited Paracetamol 500 mg Tablets, 1 x 1000, PL 04077/0001, (EL(19)A/38. Issued 27 November 2019. M&A Pharmachem Limited is recalling all unexpired batches as a precautionary measure because a small number of pots from some batches were found to contain discoloured tablets due to contamination with fungus (Penicillium citrinum). This is an update to alert EL(19)A/32, issued 5 November 2019.

Class 2 Medicines Recall: Sandoz Limited, Omeprazole 40 mg Powder for Solution for Infusion, PL 04416/0701 (EL(19)A/34). Issued 11 November 2019. Sandoz Limited is recalling one batch (JS1355) due to the occurrence of degradation in some vials, resulting in green discoloration of the powder in the vial, leading to increased levels of impurities/degradation products in the medicine.

Class 2 Medicines Recall: Kyowa Kirin Limited Mitomycin-C Kyowa, All Strengths (see alert for more information), (EL (19)A/33) Issued 7 November 2019. All unexpired batches of Kyowa Kirin Mitomycin-C Kyowa products are being recalled as a precautionary measure due to deviations from the aseptic manufacturing processes during the manufacture of the sterile active pharmaceutical ingredient and excipients.

Class 3 Medicines Recall: Folic Acid Tablets BP 5mg, PL 0142/5522, (EL(19)A/35). Issued 18 November 2019. Accord-UK has advised of an issue related to decommissioning of the batch HU57. Although there is no risk to product quality, any remaining stock should be quarantined and returned.

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