



EUROPEAN MEDICINES AGENCY  
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## Restrictions on the use of domperidone-containing medicines

On 23 April 2014, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed recommendations to restrict the use of domperidone-containing medicines. The CMDh, a medicines regulatory body representing the EU Member States, agreed that these medicines should only be used to relieve symptoms of nausea and vomiting, that doses and length of treatment should be restricted and that they should be adjusted carefully by the patient's weight where available for use in children. The recommendations were originally made by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) at its meeting of 3-6 March, after a careful evaluation of the available evidence on the benefits and risks of such medicines.

Domperidone-containing medicines have been authorised nationally in individual Member States of the EU for the treatment of nausea and vomiting of various causes but also for the management of symptoms such as bloating, discomfort and heartburn.

The review of domperidone was carried out at the request of the Belgian medicines authority over concerns about the medicine's effects on the heart. The injectable form of domperidone was withdrawn in 1985 because of such side effects. Serious effects on the heart with domperidone, including prolongation of the QT interval (an alteration of the electrical activity of the heart) and arrhythmias (unstable heartbeats), have previously been evaluated by the EMA and the product information updated with relevant warnings. However, cases of heart problems in patients using the medicine continued to be reported, and the PRAC was therefore asked to examine whether the benefits still outweighed the risks for these medicines in their approved uses and forms, and whether their marketing authorisations should be maintained or changed across the EU.

The CMDh confirmed by majority the PRAC recommendation that domperidone-containing medicines should remain available and may continue to be used in the EU for the management of the symptoms of nausea and vomiting, but that the recommended dose should be reduced to 10 mg up to three times daily by mouth for adults and adolescents weighing 35 kg or more. These patients may also be given the medicine as suppositories of 30 mg twice daily. Products licensed in children and adolescents weighing less than 35 kg should be given by mouth at a dose of 0.25 mg per kg bodyweight up to three times daily. Measuring devices will be included with liquid formulations to allow accurate dosing by bodyweight. The medicine should not normally be used for longer than one week.



Domperidone will no longer be authorised to treat other conditions such as bloating or heartburn. It must not be given to patients with moderate or severe impairment of liver function, or in those who have existing abnormalities of electrical activity in the heart or heart rhythm, or who are at increased risk of such effects. In addition, it should not be used with other medicines that have similar effects on the heart or reduce the breakdown of domperidone in the body (thus increasing the risk of side effects). The product information has been amended appropriately. Products supplying a dose of 20 mg by mouth, and suppositories of 10 or 60 mg are no longer recommended for use and should be withdrawn, as should combination products with cinnarizine (an antihistamine) where available.

Although the scope of the review did not cover use outside the licensed indications (off-label use) the principles behind these recommendations should be considered whenever domperidone is used.

As the CMDh position was adopted by majority vote, it was sent to the European Commission, which endorsed it and issued a final legally binding decision valid throughout the EU.

### **Information to patients**

- Domperidone is a medicine that has been used for various stomach and digestive problems. There have been concerns that it might increase the risk of side effects on the heart, including dangerously irregular heartbeats in some patients.
- Because a review has shown that the risks of domperidone are greatest at high doses or when it is used for a longer period, the medicine should only be approved for use in low doses to treat symptoms of nausea and vomiting (feeling or being sick). Treatment should generally only be given for up to one week.
- The recommended dose in adults is 10 mg by mouth up to three times a day, or 30 mg as a suppository twice a day. Where suitable products are available for children, doses should be calculated depending on bodyweight and given with a device that allows accurate measuring. Some products will be withdrawn from the market because their strength does not match the new doses.
- There is no good evidence to support the use of domperidone for other conditions such as bloating and heartburn, and so it is no longer authorised to treat these conditions.
- Patients with certain existing heart problems, or who are taking certain other medicines that enhance the effects of domperidone or reduce its breakdown in the body, should not take domperidone.
- Patients or carers who have any concerns should speak to a healthcare professional. Those who are taking domperidone long-term or in higher doses, or for conditions other than nausea and vomiting, should consult their doctor at their next scheduled appointment or speak to their pharmacist to discuss their treatment.

### **Information to healthcare professionals**

- A review of the evidence confirms a small increased risk of serious cardiac adverse drug reactions related to the use of domperidone, including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death. A higher risk was observed in patients older than 60 years, adults taking daily oral doses of more than 30 mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly.
- The benefit-risk balance of domperidone remains positive in the relief of the symptoms of nausea and vomiting. The available evidence of efficacy was not sufficient to support its use for other indications.

- Domperidone should be used at the lowest effective dose for the shortest possible duration. The maximum treatment duration should not usually exceed one week.
- The new recommended dose in adults (and adolescents  $\geq 35$  kg where licensed) is 10 mg orally up to three times daily (maximum dose of 30 mg daily). Adults may also be given 30 mg twice daily rectally as suppositories.
- Where suitable domperidone products are available for children, the recommended dose is 0.25 mg/kg bodyweight up to three times daily by mouth. In order to accurately measure doses to paediatric patients, oral suspensions should be given using an adapted graduated oral syringe.
- Domperidone products are contraindicated in patients with severe hepatic impairment, conditions where cardiac conduction is, or could be, impaired or where there is underlying cardiac disease such as congestive heart failure, and when co-administered with QT-prolonging medicines or potent CYP3A4 inhibitors.
- Formulations not consistent with the new dosage recommendations will be withdrawn from the market, as will combinations of domperidone with cinnarizine. The product information for domperidone-containing products has been updated, and a letter has been sent to healthcare professionals explaining the new recommendations.

These recommendations are based on careful consideration of data on the safety and efficacy of domperidone from various sources. This comprised non-clinical and clinical data, both published and unpublished, including a thorough QT study, cumulative review of case reports of cardiac disorders and vascular investigations from the safety databases for domperidone products, pharmacoepidemiological studies, and published and unpublished efficacy studies.

- Overall there was sufficient evidence to support the use of oral domperidone 10 mg up to three times a day in a general indication of treatment of nausea and vomiting in adults. There were limited data to support paediatric use in this indication, and although the mechanism of action is not expected to differ between adults and children studies to provide further data to support efficacy in the paediatric population have been requested.
- Data in support of other indications were extremely limited. In particular, there was little evidence in support of the long-term efficacy of domperidone in dyspepsia and gastro-oesophageal reflux disorder. The benefits in these indications were therefore not considered to outweigh the risk.
- Although the results of the thorough QT study with domperidone indicate that it does not significantly prolong the QTc interval when administered to healthy subjects at 10 mg and 20 mg four times daily, there are limitations in the study that restrict the conclusions that can be drawn.
- A review of the safety database of the originator product involving 342 serious reports of cardiac events or vascular investigations highlighted the high frequency of associated cardiovascular risk factors, cardiovascular history, and concomitant medications associated with cardiac arrhythmias in the patients concerned. Of 57 reported cardiovascular fatalities, 27 had other risk factors, while 13 had either an implausible relationship to domperidone administration or an alternative aetiology. In general, safety reviews indicate that about 40% of such reports are in patients over 60 years of age.
- A significant number of cases have been reported with concomitant or co-suspect medication known to prolong QT interval, CYP3A4 inhibitors, or potassium-wasting diuretics. This is in line with the data coming from drug-drug interaction studies, and from spontaneous reporting. Appropriate risk minimisation measures have therefore been included in the product information to address this issue.

- Epidemiological studies mostly suggest that domperidone exposure was associated with an increase in risk for sudden cardiac death or ventricular arrhythmia. Some of these studies also supported a greater risk in patients over 60 years of age or who were taking high doses (over 30 mg/day).

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### **More about the medicine**

Domperidone-containing medicines have been authorised in most EU Member States via national procedures since the 1970s and are widely available as over-the-counter or prescription-only medicines. They are available as tablets, oral suspension and suppositories under various trade names (such as Motilium). A combination product with cinnarizine (an antihistamine) is available in some Member States for the treatment of motion sickness.

Domperidone works by blocking receptors for the neurotransmitter dopamine found in the gut and in the part of the brain linked to vomiting. This helps to prevent nausea (feeling sick) and vomiting.

### **More about the procedure**

The review of domperidone was initiated on 1 March 2013 at the request of the Belgian medicines authority, the Federal Agency for Medicines and Health Products (FAGG-AFMPS), under Article 31 of Directive 2001/83/EC.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority vote, the CMDh position was sent to the European Commission, which endorsed it and issued a final legally binding decision valid throughout the EU on 1 September 2014.

### **Contact our press officers**

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