Domperidone: new recommendations to minimise the cardiac risks

Dear Healthcare Professional,

This letter is to inform you on the recent recommendations to minimise the cardiac risks of domperidone after the recent review on the benefits and risks of the product. As of 4th September 2014, domperidone is only available as a Prescription Only Medicine. This letter is being sent in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency.

Summary

- The benefit/risk balance of domperidone remains positive in the relief of the symptoms of nausea and vomiting in adults and adolescents and children.
- This review confirms a small increased risk of serious cardiac adverse drug reactions related to the use of domperidone. A higher risk was observed in patients older than 60 years, those taking daily doses of more than 30 mg, and those taking QT-prolonging drugs or CYP3A4 inhibitors concomitantly.
- 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 doses are:
    - For adults and adolescents ≥ 35 kg:
      10 mg up to three times daily with a maximum dose of 30 mg per day.
    - For children and adolescents < 35 kg:
      0.25 mg/kg body weight per intake up to three times daily with a maximum dose of 0.75 mg/kg body weight per day.

- Domperidone products are now contraindicated in patients with severe hepatic impairment, conditions where the cardiac conduction intervals are impaired or could be affected and underlying cardiac diseases as congestive heart failure, when co-administered with QT-prolonging drugs or potent CYP3A4 inhibitors.

Further information

Domperidone containing products have been authorised nationally in several EU member states since the 1970s and have been available in the United Kingdom under the trade name Motilium and as the generic, domperidone. The indications vary slightly between the different EU member states.

The cardiac risks of medicinal products containing domperidone have been under monitoring for several years at national and EU levels. The product information of domperidone containing products has been updated in recent years to reflect the associated risk of QTc prolongation and serious ventricular arrhythmia.

Since then, new cases of serious cardiac adverse reactions related to domperidone use have continued to be reported, leading the Belgian medicines agency to trigger a European re-evaluation of the cardiac risks in the context of the benefits in order to determine whether the marketing authorisations for
domperidone-containing products should be maintained, varied, suspended or withdrawn across the EU.

This review confirmed the risk of serious cardiac adverse drug reactions related to domperidone use including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death. Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, those taking daily doses of more than 30 mg, and in those taking other QT-prolonging drugs or CYP3A4 inhibitors concomitantly.

Based on available data, it is considered that the efficacy of domperidone is established in the relief of nausea and vomiting symptoms, and not established in other indications.

Overall, the benefit/risk balance of domperidone remains positive only for oral formulations (oral solid formulations dosed at 10 or 5 mg and oral solution) and adult suppositories (30 mg).

Finally, it was concluded that risk minimisation measures are necessary in order to improve the benefit/risk balance including restricted indications, use of lower doses, shorter treatment duration, addition of contraindications, warning and precautions.

In addition, in order to accurately measure and administer the doses to paediatric patients, oral suspensions should be given using an adapted graduated oral syringe. The UK pack does not currently contain a syringe and UK healthcare professionals are requested to consider supplying a suitably graduated syringe when the product is to be used for children under 35kg, until one becomes available in pack.

The Product Information of all domperidone containing products will be updated to reflect these data.

Call for reporting
This medicinal product is subject to additional monitoring. This allows for quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events through the Yellow Card Scheme. The easiest and quickest way to report is online at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available:
- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back if the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates and product brand name.

Suspected adverse events should also be reported to the relevant Marketing Authorisation holder. Contact point details for further information are given in product information for the medicine (SmPC and Package Leaflet).
Annex  The changes that will be made to the SmPC for domperidone products is attached in the annex. This information is being provided jointly by the Marketing Authorisation holders listed below. Contact details are provided if you wish to request further information.

<table>
<thead>
<tr>
<th>Company</th>
<th>Product name</th>
<th>Contact email</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zentiva</td>
<td>Motilium 10mg Tablets,</td>
<td><a href="mailto:UK-drugsafety@sanofi.com">UK-drugsafety@sanofi.com</a></td>
<td>01483 554242</td>
</tr>
<tr>
<td></td>
<td>Domperidone 1mg/ml Suspension</td>
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<tr>
<td>Athlone Pharmaceuticals Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:adonohoe@athlene-laboratories.com">adonohoe@athlene-laboratories.com</a></td>
<td>00353 86 0226712</td>
</tr>
<tr>
<td>Bristol Laboratories Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:info@bristol-labs.co.uk">info@bristol-labs.co.uk</a></td>
<td>01442 200922</td>
</tr>
<tr>
<td>Co-Pharma Limited</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:peter@co-pharma.co.uk">peter@co-pharma.co.uk</a></td>
<td>01923 255580</td>
</tr>
<tr>
<td>Focus Pharmaceuticals Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:medinfo@focuspharma.co.uk">medinfo@focuspharma.co.uk</a></td>
<td>01283 495280</td>
</tr>
<tr>
<td>Manx Healthcare Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:safety@manxhealthcare.com">safety@manxhealthcare.com</a></td>
<td>01926 482511</td>
</tr>
<tr>
<td>Medreich PLC</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:Info@medreich.co.uk">Info@medreich.co.uk</a></td>
<td>02088311580</td>
</tr>
<tr>
<td>Milpharm Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:medinfo@aurobindo.com">medinfo@aurobindo.com</a></td>
<td>0208 839 0959</td>
</tr>
<tr>
<td>Wockhardt UK Ltd</td>
<td>Domperidone 10mg Tablets</td>
<td><a href="mailto:Drug.Safety@wockhardt.co.uk">Drug.Safety@wockhardt.co.uk</a></td>
<td>01978 661261</td>
</tr>
</tbody>
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