EV) 593475

NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EC made by Belgium-FAMHP

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s) Active Substance(s)/Therapeutic class	All domperidone containing products and strengths
Marketing Authorisation Holder(s)	Various

Domperidone is commonly used across Europe. Belgium is the Reference Member State (RMS) for the innovator product Motilium® since 2003.

Domperidone is indicated in adults for the relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents and in children for the relief of the symptoms of nausea and vomiting.

In the mid 1980s a possible association of QT-prolongation, and cardiac adverse events, was identified when high and rapidly administered intravenous doses of domperidone, were used as an anti-emetic during cytotoxic treatment in cancer patients.
On recognition of this possible association, the intravenous formulation was voluntarily withdrawn worldwide by the Marketing Authorisation Holder, and no intravenous formulations have been manufactured since 1985.
Over the last years, cardiovascular events including risk of QT-prolongation, arrhythmia, sudden death have been discussed by the Pharmacovigilance Working Party (PhVWP). This led to changes to the product information agreed by the PhVWP in October 2011. The MAH of the innovator was also requested to conduct a pharmacoepidemiological study and a thorough QTc study.

Since then, new cases of cardiotoxicity related to domperidone have been reported. Some of these are included and assessed in the PSUR Work Sharing procedure covering the period January 2009 to January 2012 and for which Belgium acts as P-RMS. In its assessment report, Belgium, notably, proposed to contra-indicate the use of domperidone in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

Furthermore, in 2012 a procedure referred to in article 45 of Regulation 1901/2006/EC, as amended, was performed and a conclusion was reached that high-dose paediatric regimen of domperidone was no longer considered as acceptable and therefore the section 4.2 paediatric posology of the SmPC should be modified.

In light of the above, Belgium considers that it is in the interest of the Union to refer domperidone-containing medicinal products to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether the balance of benefits and risks is positive for these products in the approved indications and whether the marketing authorisation for medicinal products

containing domperidone should be maintained, varied, suspended or withdrawn.

A draft list of questions to be submitted to the MAHs is annexed.

Signed [redacted]

Date 01/03/2013

afmps
agence fédérale des médicaments et des produits de santé
Entité/Division/Unité/Cellule

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26 February 2013

Domperidone cardiac risk LOQ to be addressed by the Marketing Authorisation Holders of domperidone containing products.

The marketing authorisation holders (MAHs) for domperidone containing medicinal products are requested to provide the following:

Question 1

How is domperidone used?

Please provide:

a) Information on the currently authorised domperidone-containing products in the different member states and their current marketing and legal (i.e. prescription vs. non-prescription) status, including information about the indication(s), doses, contraindications, warnings and precautions, and undesirable effects included in the Summary of Product Characteristics and the package leaflet. Please tabulate the main differences between the SmPCs/package leaflets in the different EU Member States.

The specific information about treatment duration and the maximum daily dose present in the SmPC should be specified.

b) Information on sales figures and estimated patient exposure for domperidone. This should include a yearly breakdown of sales and exposure over the last 10 years for each Member State.

c) Data on the way domperidone is used in clinical practice including information on daily dose and duration of treatment.

d) Information on the off-label use of domperidone especially in the context of insufficient lactation, diabetic gastroparesis and gastro-esophageal reflux.

Question 2

What is the evidence for the risk of cardiac events associated with domperidone?

Please provide all cardiac safety information available since the launch of your medicinal product. This should include non clinical, clinical data as well as epidemiological studies and cases reported in the literature. A cumulative review of all cases reports should also be provided. For this purpose, all the MedDRA Preferred Terms (PTs) within the System Organ Class (SOC) Cardiac disorders, and the High Level Group Term (HLGT) Cardiac and vascular investigations (excl enzyme tests), reported for the selected suspected or interacting domperidone products should be provided and causality assessment should be performed.

Question 3

What is your analysis of the balance of risks and benefits of domperidone?

Please provide a benefit/risk assessment of domperidone in its licensed indication(s), and whether this is modified by the cardiac risk in any indications or populations.

Question 4

Please provide proposals and justification with supportive evidence for any measures including changes to the SPC/PIL which may improve the benefit/risk of domperdione and how their effectiveness should be monitored.