Annex II

Scientific conclusions and grounds for revocation or variation to the terms of the marketing authorisations, as applicable, and detailed explanation for the differences from the PRAC recommendation

Scientific conclusions

The CMDh considered the below PRAC recommendation with regards to domperidone-containing medicinal products:

1 - PRAC recommendation

Overall summary of the scientific evaluation by PRAC

A possible association between domperidone and QT-prolongation and cardiac adverse events was identified in the mid-1980s, when high and rapidly administered intravenous doses were used as an anti-emetic during cytotoxic treatment in cancer patients. As a consequence, the intravenous formulation was withdrawn worldwide.

Subsequently, cardiovascular events including risk of QT-prolongation, arrhythmia and sudden cardiac death in association with other pharmaceutical forms of domperidone have since been discussed at the European level by the Pharmacovigilance Working Party (PhVWP). In October 2011 the PhVWP agreed on amendments to the product information, and the Marketing Authorisation Holder of the originator product was requested to conduct a pharmacoepidemiological study and a thorough QTc study. However new cases of cardiotoxicity continued to be reported.

In light of the above, on 01 March 2013 Belgium informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their decision to trigger an Art. 31 referral procedure to ask for the PRAC's recommendation on whether the balance of benefits and risks for these products is still positive in the approved indications, and whether the marketing authorisations for medicinal products containing domperidone should be maintained, varied, suspended or withdrawn.

Domperidone is a peripheral dopamine D_2-receptor antagonist with gastrokinetic and anti-emetic properties. It is used in the treatment of symptoms of nausea and vomiting of variable origin. It exerts its action via inhibition of dopamine receptors in the human gut, and in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema.

Domperidone is commonly used across Europe since 1970s when it was first time authorized via national procedures. The International Birth Date for domperidone has been designated as March 1978, based on the first approval of domperidone in Belgium.

The authorized indications of domperidone, as listed in the Company Core Data Sheet of the originator, are presented below:

- The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-oesophageal reflux, and oesophagitis:
    - epigastric sense of fullness, early satiety, feeling of abdominal distension, upper abdominal pain
    - bloating, eructation, flatulence
    - nausea and vomiting
    - heartburn with or without regurgitations of gastric contents in the mouth
- Nausea and vomiting of functional, organic, infectious or dietetic origin
- Nausea and vomiting induced by:
    - radiotherapy or drug therapy

- dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease

Domperidone is marketed in several formulations, for oral or rectal administration under various trade names. A formulation for intravenous (IV) administration was discontinued in 1985.

Domperidone is authorised also as a fixed-dose combination product with cinnarizine and indicated for the prevention and treatment of symptoms associated with motion sickness.

Domperidone-containing medicines are available as over-the-counter (OTC) or prescription-only medicines (POM).

When considering existing data in support of the efficacy of domperidone, the PRAC concluded that overall there is sufficient evidence[1,2,3] in support of the use in a general indication in the relief of symptoms of nausea and vomiting in adults.

The data in support of the paediatric use in relief of symptoms of nausea and vomiting is limited. However, it is not expected that the mechanism of action will differ between adults and children, and there is in some Member States long-lasting clinical experience with this product in children. The PRAC nevertheless considered appropriate that further studies be performed to document the efficacy of domperidone in children in this indication and in the newly recommended posology.

For all indications other than "relief of symptoms of nausea and vomiting", there is extremely limited evidence of efficacy of domperidone, and therefore the potential benefits are considered to be outweighed by the identified cardiac risk.

The available clinical and non-clinical data consistently indicates that there is an increased risk of serious and potentially life-threatening cardiac adverse drug reactions associated with domperidone use. The risks are increased in patients who are over 60 years of age, who are using high doses and/or who are using concomitant QT-prolonging drugs or products that can increase plasma levels of domperidone. It is therefore important that the risk is minimised by restricting the maximum dose (10 mg up to 3 times a day for adults and adolescents 12 years of age and older and weighing ≥ 35 kg), limiting treatment duration to the shortest necessary to control symptoms and contraindicating other drugs that are also known to prolong the QT-interval. It should also be contraindicated in patients with moderate to severe hepatic impairment and in co-administration with potent CYP3A4 inhibitors, due to the expected increase in plasma levels of domperidone.

As a consequence of the new maximum recommended doses, the PRAC considered that certain formulations such as tablets dosed at 20 mg and suppositories dosed at 60 mg have a negative benefit-risk balance and should therefore be revoked. The extrapolation of existing pharmacokinetic data allows for a conclusion that the 30 mg suppository administered twice a day should be equivalent to the 10 mg oral formulation administered 3 times a day. However it is important that this be confirmed in an appropriate pharmacokinetic study.

The PRAC also considered that the combination domperidone/cinnarizine, which contains 15 mg domperidone (higher than the newly recommended individual dose), has a negative benefit-risk balance. In this respect, the PRAC further noted that not only the efficacy data is limited but it does not actually demonstrate the superiority of the combination over the single component product. Under

[1] De Loose F. Clinical Research Report. Double-blind comparison of domperidone with placebo in the treatmentof chronic postprandial gastrointestinal distress: A multicenter study. Janssen Research Products Information Service. Unpublished internal report. Jul 1980. Doc ID:LMD21025;EDMS-ERI-47362001

[2] Englert W, Schlich D. A double-blind crossover trial of domperidone in chronic postprandial dyspepsia. Postgrad Med J. 1979;55:28-29. Doc ID:LMD13791;EDMS-ERI-62039099.

[3] Von Matushka N. Clinical Research Report. A multicentre double-blind evaluation of domperidone in the treatment of postprandial dyspepsia. Janssen Clinical Research Report April 1979. Doc ID:LMD18089;EDMSERI-47380126.

these circumstances patients should not be exposed to the additional risk associated to a combination product.

Domperidone is not approved in all Member States for paediatric use in the subpopulation under 12 years of age and adolescents weighing <35 kg. Whenever approved, it is noted that the currently recommended posology varies between products, ranging from 0.25-0.5 mg/kg 3 to 4 times a day. For the reasons mentioned above, it is critical that patients are given the lowest possible effective dose and the PRAC considered that a recommendation for 0.25 mg/kg up to 3 times a day was appropriate.

The PRAC also noted that the rectal formulations dosed at 10 mg and approved for paediatric use do not allow for the recommended dose adjustment according to body weight, and therefore are likely to result in exposing paediatric patients to a dose higher than the newly recommended. Therefore the PRAC concluded that the benefit-risk balance of rectal formulations for paediatric patients is negative due to the potential for overdose. Whenever available, paediatric patients should make use of other formulations that allow for more accurate dosing (e.g. oral solution) and these should be supplied with an appropriate measuring device.

Off-label use of domperidone is known to exist for conditions such as GERD, gastroparesis and stimulation of lactation. In view of the cardiac risk, off-label use should be monitored.

Grounds for the revocation / variation to the terms of the marketing authorisation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for domperidone-containing medicinal products.
- The PRAC considered the totality of the data submitted in support of the safety and efficacy of domperidone.
- The PRAC considered that domperidone is associated with an increased risk of serious cardiac adverse drug reaction, including QT prolongation and sudden cardiac death. The risks are increased in patients who are over 60 years of age, who are using high doses and/or who are using concomitant QT-prolonging drugs or products that can increase plasma levels of domperidone.
- The PRAC considered that the risk of serious cardiac adverse drug reactions can be minimised by using lower doses of domperidone, limiting treatment duration and contraindicating treatment for patients at particularly high risk (patients with moderate or severe hepatic impairment, patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure) and patients concurrently taking QT-prolonging drugs or potent CYP3A4 inhibitors. Therefore some of the high dose formulations can no longer be recommended.
- The PRAC noted that the rectal formulations approved for paediatric use do not allow for the necessary recommended dose adjustment according to body weight, and therefore are likely to result in exposing paediatric patients to a dose higher than recommended.
- The PRAC noted that, in the combination domperidone/cinnarizine, domperidone is dosed at a 15 mg which is higher than the newly recommended individual dose. In addition, the data supporting the efficacy of the combination domperidone/cinnarizine for motion sickness are limited, do not demonstrate the superiority of the combination over the single component product and therefore do not justify exposing patients to the additional risk associated to a combination product.
- The PRAC was of the opinion that existing data, although limited, are indicative of efficacy in the indication ‘relief of symptoms of nausea and vomiting’.

- The PRAC was also of the opinion that existing data on the efficacy of domperidone in indications other than 'relief of symptoms of nausea and vomiting' are very limited, and therefore the potential benefit is outweighed by the cardiac risk.
- The PRAC considered that the data supporting the efficacy of domperidone in the paediatric population are limited and recommended that further data be generated to confirm the efficacy in this patient population.
- The PRAC considered that the pharmacokinetic data supporting the rectal formulations is limited, and therefore recommended that further data be generated to allow for a comparison between the oral and rectal formulations.
- In view of the available data the PRAC concluded, subject to the amendments to the product information and implementation of other risk minimisation measures, that the benefit-risk balance of domperidone-containing products:
    - Is favourable in the relief of the symptoms of nausea and vomiting.
- In view of the available data the PRAC also concluded that the benefit-risk balance of domperidone-containing products:
    - Is not favourable in all other currently approved indications.
    - Is not favourable for high dose oral formulations (higher than 10 mg).
    - Is not favourable for high dose rectal formulations (60 mg) or rectal formulations approved for paediatric use (10 mg).
    - Is not favourable for the combination domperidone/cinnarizine.

Therefore, in accordance with Article 116 of Directive 2001/83/EC, the PRAC recommends:

- The revocation of the marketing authorisations for:
    - oral formulations dosed higher than 10 mg
    - rectal formulations dosed at 10 mg and 60 mg
    - combination products containing domperidone/cinnarizine
- The variation to the terms of the marketing authorisation for the remaining domperidone-containing medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation. Oral liquid formulations shall be supplied with an appropriate measuring device.

The PRAC, as a consequence, concluded that the benefit-risk balance of domperidone-containing medicinal products remains favourable subject to the conditions to the marketing authorisations, and taking into account the amendments to the product information and other risk minimisation measures recommended.

2 – Detailed explanation for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. Taking into account the Commission Decision of the Article 30 Procedure on Domperidone the CMDh confirmed that the benefit-risk ratio for indication 'relief of the symptoms of nausea and vomiting' (including in the paediatric population) remains positive. However, the CMDh considered that changes were necessary to proposed conditions to the Marketing Authorisations (Annex IV). The CMDh considered the request from one MAH with regards to the timelines to fulfil some of the conditions as proposed by the PRAC. The CMDh agreed to:

- Extend the timeframe for the submission of the final study report on condition 1 (generation of paediatric efficacy data). However, in order to ensure that the study will provide relevant data, MAHs are requested to submit the protocols for agreement to the National Competent Authorities. In addition, in order to ensure that National Competent Authorities are informed of the study progress, MAHs are required to submit yearly updates on progress with recruitment to the study. The CMDh highly recommends that MAHs collaborate in order to avoid unnecessary duplication of studies.
- Extend the timeframe for the submission of the final study report on condition 2 (pharmacokinetic study to generate data to allow for a comparison between the rectal and oral formulations).
- The CMDh considered that the drug utilisation study in condition 3 needs to be performed in more than one Member State in order to achieve its goal of monitoring off-label use.

In addition, the CMDh took the opportunity to introduce the following clarification to the description of the products for which revocation is recommended:

- The revocation of the marketing authorisations for:
  - oral formulations at a strength higher than 10 mg
  - rectal formulations at 10 mg and 60 mg strengths
  - combination products containing domperidone/cinnarizine

Minor amendments were also introduced in the Product Information for clarity.

CMDh position

The CMDh, having considered the PRAC recommendation dated 6 March 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached a position on the variation or revocation as applicable of the marketing authorisations of domperidone-containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.