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Pharmacovigilance Risk Assessment Committee (PRAC)

# Assessment report

Procedure under Article 31 of Directive 2001/83/EC

Domperidone-containing medicinal products

International non-proprietary name: domperidone

Procedure number: EMEA/H/A-31/1365

## Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

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 As a consequence, the intravenous formulation was withdrawn worldwide.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 Article 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the marketing authorisations for medicinal products containing domperidone should be maintained, varied, suspended or withdrawn.

# 2. Scientific discussion

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).

## *2.1. Non-clinical aspects*

The effects of domperidone have been investigated in a comprehensive battery of in vitro and in vivo assays in line with the recommendations of ICH S7B (core battery and follow up studies). An overview of exposure (IKr attenuation) and safety margins as compared to the mean drug plasma levels at Cmax during steady state at the new maximum recommended dose of 30 mg/day (total Cmax of 13.5 ng/ml and free Cmax of 0.945 ng/ml(2.2 nM)) in man are provided below:

- Ratios for the concentration of domperidone, attenuating IKr in hERG transfected cells with the mean free drug plasma levels at Cmax during steady state in man range between 25.9- and 46.8-fold.
- Potencies for attenuating IKr were substantially lower for the 3 metabolites than for domperidone (ratio >718-fold).
- Ratios for the concentration of domperidone, without effect on APD in isolated rabbit Purkinje fibres, canine Purkinje fibers and papillary muscles, guinea pig atrium, and guinea pig papillary muscles, with the mean free drug plasma levels at Cmax during steady state in man amount to 45.4-fold.
- Ratios for the concentration of domperidone, without effect in the SCREENIT (isolated Langendorff rabbit heart) model, with the mean free drug plasma levels at Cmax during steady state in man amount to 45.4-fold. The Lawrence et al (2006)[1] publication demonstrates that ratios for the concentration of domperidone, without effect in the SCREENIT (isolated Langendorff rabbit heart) model, with the mean free drug plasma levels at Cmax during steady state in man amount to 8.6-fold as the no effect level is identified at 19 nM. At a concentration of 190 nM triangulation, instability and reverse use dependency are observed.
- The effects of domperidone have been investigated in a modified isolated rabbit heart preparation (SCREENIT system), involving exposure of the preparation following a 10 minute baseline to 5 consecutively tripled concentrations for 30 minutes. The lack of validation for this model and the questionable reliance on the control values generated following different testing schemes is noted. If the results from these recent publications would be taken into account, this would entail that by setting the no effect concentration at 30 nM, the ratio for the free plasma concentration of domperidone, without significant effects on the TRIaD proarrhythmic parameters effect with the mean free drug plasma levels at Cmax during steady state in man amounts to 13.6-fold.
- The ratio for the free plasma concentration of domperidone administered orally, without QT prolonging effect in the anaesthetised and the conscious dog model, with the mean free drug plasma levels at Cmax during steady state in man amount to, respectively, 145.0-fold and 21.7-fold.

[1] Lawrence C.L., Bridgland-Taylor M.H., Pollard C.E., Hammond T.G. and Valentin J.P. A rabbit Langendorff heart proarrhythmia model: Predictive value for clinical identification of Torsades de Pointes. Br J Pharmacol. 2006;149 (7): 845-60. Doc LMD N226280.

- The ratio for the free plasma concentration of domperidone, without torsadogenic effect in the methoxamine-sensitised rabbits (411 ng/ml) following intravenous administration, with the mean free drug plasma levels at Cmax during steady state in man amounts to 435.0-fold.
- The effects of slow intravenous infusions of domperidone were evaluated in an anaesthetized guinea pig model. There were no effects on QTcB at a total plasma concentration of 45.4 ng/mL (domperidone + metabolites; 3.4X safety margin).
- The no effect dose following i.v. administration of domperidone to the anaesthetised dog, can be set at the total cumulative dose of 1.19 mg/kg, which entails a free maximal plasma concentration of 61 ng/ml. The ratio for the free plasma concentration of domperidone, without QTcB prolonging effects, with the mean free drug plasma levels at Cmax during steady state at the new maximum recommended dose of 30 mg/day in man amounts to 64.6-fold.

Non-clinical pharmacodynamic interaction studies failed to demonstrate synergism but rather pointed to a (partial) additive effect that is influenced by the order of administration.

Safety margins range between 3.4-fold and 435-fold depending on the test model. It should be noted that the relevance of the in vivo guinea pig model (intravenous administration of domperidone) for an orally administered drug is questionable and that the validity of the modified isolated Langendorff rabbit heart model is questionable. Non-inclusion of the results obtained in both aforementioned test models if justified would now increase safety margins ranging from 8.6-fold up to 435-fold. In addition hERG channel inhibition IC50s are noted at 25.9- and 46.8-fold human free plasma exposure at 20 mg/kg b.i.d.

Based upon these data it can clearly be concluded that domperidone has the potential to induce QT-prolongation. The non-clinical safety margins should be interpreted with caution taking into account the test model considered (in vitro, in vivo, species, administration route, etc) and taking into account that safety margins for absence of torsadogenic behaviour are high.

## *2.2. Clinical aspects*

### 2.2.1. Pharmacokinetic properties

#### *Absorption*

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver.

Although in normal subjects, domperidone's bioavailability is enhanced when taken after a meal, reduced gastric acidity impairs the absorption of domperidone base. Oral bioavailability of domperidone base is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

The bioavailability of a 60-mg suppository after single or repeated dosing is approximately 65% of 80 mg of oral tablets given over 24 hours. After rectal administration of 60-mg suppositories, mean domperidone plasma concentrations between 20 and 40 ng/mL are maintained from approximately 0.5 to 5 hours after single- and multiple-dose administration. Following single-dose administration, mean peak plasma levels of 60-mg suppositories are 89% of that of two 10-mg oral tablets, but the mean dose-normalized rectal bioavailability relative to oral tablets is 64%. Following multiple-dose administration, mean peak plasma levels and dose normalized bioavailability of 60 mg suppositories

administered every 12 hours are 63% and 66%, respectively, of two 10-mg oral tablets administered every 6 hours.

Although data is not available for the 30 mg suppository, taking into account linear pharmacokinetics[2], it can be deduced that a 30 mg suppository b.i.d. results in an exposure over 24 hours comparable to that obtained by a 10 mg t.i.d. oral dose.

***Distribution***

Oral domperidone does not appear to accumulate or to induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/mL after 2 weeks oral administration of 30 mg per day was almost the same as that of 18 ng/mL after the first dose. Domperidone is 91% to 93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

***Metabolism***

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

***Excretion***

Urinary and faecal excretions amount to 31 and 66% of the oral dose, respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion).

The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects, but is prolonged in patients with severe renal insufficiency.

***Special Populations***

*Hepatic impairment*

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment have not been studied.

*Renal impairment*

In subjects with severe renal insufficiency (serum creatinine >6 mg/100 mL, ie, >0.6 mmol/L) the half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in subjects with normal renal function. Very little unchanged drug (approximately 1%) is excreted via the kidneys.

*Paediatric patients*

Based on limited pharmacokinetic data, domperidone plasma concentrations in preterm neonates were consistent with those reported in adults.

*Paediatric exposure through breast milk*

[2] Huang, Y.-C., Colaizzi, J. L., Bierman, R. H., Woestenborghs, R. and Heykants, J. J. P. (1986), Pharmacokinetics and Dose Proportionality of Domperidone in Healthy Volunteers. Journal of Clinical Pharma, 26: 628–632.

Studies of domperidone in insufficient lactation[3,4,5,6] have measured domperidone excretion in breast milk at steady state. Assuming a total milk intake of 0.15 l/Kg/d, the maximal absolute infant dose of domperidone is estimated to 0.51 µg/kg/d, with a maternal dose of 30 mg/d, and 1.035 µg/kg/d with a maternal dose of 60 mg. The maximal relative infant dose (%) is estimated to about 0.1 % of the maternal weight-adjusted dosage, which is considered low.

## 2.2.2. Safety

In its assessment, the PRAC considered all the data submitted to the Committee from different sources. A summary of the most relevant data is included below:

***Thorough QT study***

A randomized, double-blind, 4-way crossover, placebo and positive-controlled, single-centre, single- and multiple-dose study (DOMDYP1001) according to the ICH-E14 guideline was conducted to assess the effects of single and multiple doses of domperidone on the QTc interval duration in healthy adult subjects, at the recommended 10 mg q.i.d. and 20 mg q.i.d. doses of domperidone.

The results of the study showed no clinically relevant effect of domperidone on QTc when domperidone was administered as single or multiple q.i.d. doses of 10 mg or 20 mg, i.e., up to a total daily dose of 80-mg domperidone. A brief summary of this study is presented below.

*Study design*

Forty-four subjects between 18 and 55 years of age were enrolled in the study and were randomized to one 1 of 4 treatment sequence groups and received the following 4 treatments, 1 in each period:

**Table 1 Thorough QT study design**

| Treatment | Description of Treatment |
|---|---|
| A (Domperidone 10 mg) | Domperidone 10 mg q.i.d + domperidone-placebo q.i.d on Days 1 to 3 and a single dose on Day 4; moxifloxacin-placebo single dose on Day 1 a.m. |
| B (Domperidone 20 mg) | Domperidone 2 x 10 mg q.i.d. on Days 1 to 3 and a single dose on Day 4; moxifloxacin-placebo single dose on Day 1 a.m. |
| C (Placebo) | 2 x domperidone-placebo q.i.d. on Days 1 to 3 and a single dose on Day 4; moxifloxacin-placebo single dose on Day 1 a.m. |
| D (Moxifloxacin) | 2 x domperidone-placebo q.i.d. on Days 1 to 3 and a single dose on Day 4; moxifloxacin 400 mg single dose on Day 1 a.m. |

*Subject information*

Forty-four subjects (32 men and 12 women) were enrolled, of which 40 subjects completed the study and 4 subjects discontinued early. At baseline, the mean (SD) for age was 43.5 (7.99) years, mean (SD) for weight was 74.63 (10.30) kg, the mean (SD) for height was 173.6 (6.88) cm and mean (SD) for body mass index was 24.7 (2.79) kg/m2. Out of the 44 subjects, 42 were White, 1 was Asian and 1 was of other race (Oriental).

*Assessments and endpoints*

Serial 12-lead ECGs were recorded in triplicate at 30, 20, and 10 minutes before dosing on Day 1, at 10 minutes before dosing (predose) on Day 4 and at 8 predefined timepoints after dosing on Day 1

[3] Hofmeyr GJ, van Iddekinge B. Domperidone and lactation. Lancet. 1983 Mar 19;1(8325):647.

[4] Hofmeyr GJ, Van Iddekinge B, Blott JA. Domperidone: secretion in breast milk and effect on puerperal prolactin levels. Br J Obstet Gynaecol. 1985 Feb;92(2):141-4.

[5] Knoppert DC, Page A, Joanne W et al. The effect of two different domperidone dosages on maternal milk production.Journal of human lactation. 2012

[6] Wan EWX, Davey K, Page-Sharp M, et al. Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. Br J Clin Pharmacol. 2008;66(2):283–289.

and Day 4 of each period. Blood samples for the determination of domperidone and moxifloxacin plasma concentrations were collected with the pharmacokinetic (PK) blood samples taken within 5 minutes after the last of the triplicate 12-lead ECG recording. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, and vital signs measurements from the screening phase through study completion, including the washout interval.

The measured QT intervals were corrected for HR using 3 correction methods (Fridericia [QTcF], Bazett [QTcB] and study-specific power [QTcP] correction). The average of the 3 sets of triplicate values obtained 30, 20, and 10 minutes before dosing on Day 1 was taken as baseline measurement for that period. The change from baseline (predose on Day 1) in QTc intervals (ΔQTc) was calculated at each timepoint after dosing. The difference in mean change from baseline, ΔΔQTc, between each dose of domperidone and placebo (Day 1 and Day 4) and between moxifloxacin and placebo (Day 1 only) was calculated at each timepoint. Moxifloxacin effect on QTc intervals served to determine assay sensitivity and assay sensitivity was convincingly demonstrated as per protocol (mean 2 to 4 hr QTcP response: 10.3 msec [90% CI: 9.4-11.2 msec]).

*Main results and conclusions*

This study was designed as a thorough QT/QTc study as it incorporated the critical elements recommended in the ICH E14 guideline (such as a randomized and double-blind study design with concurrent placebo and active group controls).

Based on the criteria set forth in the ICH-E14 guidelines, the results of the study indicate this to be a negative thorough QT study. No clinically relevant effect of domperidone on QTc was observed when domperidone was administered as single or multiple q.i.d. doses of 10 mg or 20 mg. Based on the mixed effects model for QTcP, the largest difference between domperidone and placebo in LSmeans in the change from baseline was 2.0 msec (90% CI: 0.2-3.8 msec) for the 10 mg domperidone dose on Day 1, and 3.4 msec (90% CI: 1.0-5.9 msec) for 20 mg q.i.d. domperidone on Day 4. The upper limit of the 2-sided 90% Confidence Interval did not exceed 10 msec at any dose or timepoint. Categorical outlier analysis did not indicate a signal for QTc prolongation with domperidone as there were no subjects with a change from baseline in QTcP interval at any timepoint in excess of 30 msec, and only 1 subject with QTcP interval barely >450 msec, up to 456.1 msec for domperidone 10 mg. The baseline QTcP for that subject was 443.1 msec, so the change in QTcP was only 13 msec. No clinically relevant dose-QTc response and exposure-QTc response effects were observed. Plasma concentrations of domperidone were as expected for the dosing regimens used in the study. Domperidone was safe and well tolerated at the recommended doses included in this study.

The main limitation of the study resided in the absence of a supra-therapeutic dose (typically defined as a 5-fold multiple over the recommended dose). The doses used in a TQT study should allow to cover the "worst-case" plasma concentrations likely to be achieved. The supra-therapeutic dose in TQT studies allows the simulation of exposure levels that can be attained in patients with impaired clearance of the drug or with metabolic inhibitors. The E14 guideline states that "if not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure". In this study, the inclusion of supratherapeutic doses (administered in healthy volunteers) was ethically questionable, because a potential relevant QTc prolongation was foreseen. Moreover, the use of only 2 doses of the active drug (as usually done in TQT studies) does not allow to correctly plot the dose-response curve. Hence, this data is not sufficient for building a reliable model for predicting the QTc prolongation if higher plasma concentrations are reached due to, e.g. drug-drug interactions or functional impairment.

***Drug-drug interactions***

Clinical PK interaction data are available with strong CYP3A4 inhibitors (itraconazole and ketoconazole), a strong-to-moderate CYP3A4 inhibitor (erythromycin) and weak CYP3A4 inhibitors (cimetidine and omeprazole), as seen in Table 2. When combined with strong CYP3A4 inhibitors, under maximal CYP3A4 inhibition, Cmax exposure to domperidone increased less than 3-fold. With strong-to-moderate CYP3A4 inhibition a 2.4-fold increase in Cmax was seen, and with weak inhibitors no increase in Cmax was observed.

**Table 2 Effects of CYP3A4 Inhibitors on Domperidone Exposure**

| Coadministered Drug | Dose of Coadministered Drug | Dosing of Domperidone | Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00 | | References |
|---|---|---|---|---|---|
| | | | Cmax | AUC | |
| Do not take domperidone if you are taking these medicines: | | | | | |
| Ketoconazole | 200 mg BID | 10 mg QID | 2.9 | 3.6 | DOMGBR1; 2002 |
| Itraconazole | 200 mg QD | 20 mg SD | 2.7 | 3.2 | Yoshizato et al.; 2012[35] |
| Erythromycin | 500 mg TID | 10 mg QID | 2.4 | 2.7 | DOMGAI1002; 2006 |
| No dosing adjustments required for the following: | | | | | |
| Cimetidine & sodium bicarbonate | 400 mg SD & 500 mg SD, respectively | 60 mg SD (maleate) | 0.96 | 1.19 | R33812-57 / N21026, 1980 |
| Omeprazole | 20 mg BID | 10 mg SD (base) | 0.84 | 0.94 | Zhang et al.; 2007[36] |
| | | 10 mg SD (maleate) | 1.08 | 1.06 | |

Effects of domperidone on QT interval when administered alone or in combination with strong to moderate CYP3A4 inhibitors which also prolong the QTc interval are also well studied and results of 2 drug-drug interaction studies are summarized in Table 3.

**Table 3 Effects of Domperidone on QT when Administered in Combination with Strong-to-Moderate CYP3A4 Inhibitors that also Prolong QT**

| | GBR-1 (DDI study with ketoconazole) (Δ placebo) | GAI-1002 (DDI study with erythromycin) (Δ baseline, placebo control) |
|---|---|---|
| $C_{max}$ (DOM) | 23.5 → 67.9 ng/mL (2.7x↑) | 24.1 → 57.3 ng/mL (2.4x↑) |
| $C_{max}$ (KETO/ERY) | 5.69 → 5.73 ug/mL (same) | 2.94 → 3.70 ug/mL (1.2x↑) |
| | | |
| Average Effect on QTcF | 1.5 msec (DOM, 24h mean) | 2.5 msec (DOM, 16h mean) |
| | 3.5 msec (KET, 24h mean) | 4.9 msec (ERY, 16h mean) |
| | 9.2 msec (COM, 24h mean) | 9.9 msec (COM, 16h mean) |
| | | |
| | 4th dose day 7 | 3rd dose day 5 |
| Maximum Effect on QTcF | 5.4 msec (DOM, 4h) | 5.7 msec (DOM, 1h) |
| | 9.6 msec (KET, 4h) | 8.2 msec (ERY, 4h) |
| | 15.6 msec (COM, 4h) | 13.6 msec (COM, 1h) |
| Key: DOM = domperidone; ERY = erythromycin; KETO = ketoconazole; COM = in combination | | |

With ketoconazole or erythromycin monotherapy, statistically significant increases in QTcF were observed at 1 to 4 hour timepoints during the 24-hour observation period. The maximal increase in

QTcF at any one timepoint varied from 8.6 to 9.2 msec. The 24-h average increase of QTcF ranged from 3.5 to 4.9 msec. These results suggest that ketoconazole or erythromycin as monotherapy has the potential to prolong QTcF, numerically about double as was observed for domperidone in these studies.

Concomitant administration of ketoconazole or erythromycin with domperidone resulted in 2- to 3-fold increase of domperidone Cmax. However, domperidone did not affect the pharmacokinetics of ketoconazole nor erythromycin. Following the combination treatment, a statistically significant increase in QTcF was observed at most timepoints during the 24-hour observation period with a maximal increase of 13.6 to 15.3 msec. It should be noted, however that there were large differences in QTc changes from baseline at adjacent timepoints, indicating suboptimal control of variability in these studies. The 24-hour average increase of QTcF as compared with placebo ranged from 9.2 to 9.9 msec. Based on the results of these drug interaction studies, potent CYP3A4 inhibitors which also prolong QTc such as ketoconazole or erythromycin should be avoided when taking domperidone.

***Clinical safety assessment***

A cumulative review performed using the safety database of the originator to search for all serious cases involving any event from the Cardiac Disorders SOC and Vascular investigations (excluding enzyme tests) HLGT retrieved 349 serious cases, of which 7 were excluded from assessment due to absence of patient identifiers (data lock point 31 January 2012). Among the 342 cases, more cases involved women (191 women vs. 123 men). Cases involved all the age groups including children.

**Table 4 Cumulative review of safety database of originator – distribution per age group of cases involving any event from the Cardiac Disorders SOC and Vascular investigations (excluding enzyme tests)**

| Age Group | Number of cases |
|---|---|
| 0 to 11 months | 30 |
| 12 to 23 months | 3 |
| 24 months to 5 years | 0 |
| 6 to 11 years | 5 |
| 12 to 17 years | 5 |
| 18 to 35 years | 41 |
| 36 to 50 years | 57 |
| 51 to 64 years | 68 |
| ≥65 years | 92 |
| Not reported | 41 |

The most frequently reported events were: Cardiac arrest (n=50), followed by Myocardial infarction (n=41), Electrocardiogram QT prolonged (n=39), Tachycardia (n=27), Cyanosis (n=23), Arrhythmia (n=22), Palpitations (n=20), Cardiac failure congestive (n=20), Cardiac failure (n=19), Bradycardia (n=18), Torsade de pointes (n=16), Ventricular tachycardia (n=11), Angina pectoris (n=11), and Ventricular fibrillation (n=9).

A total of 232 cases have been reported with co-suspect/concomitant medications and including medications known to prolong QT interval, CYP3A4 inhibitors, and/or potassium–wasting diuretics.

The outcomes of the 439 cardiac events were the following: resolved/resolving (n=230); followed by not reported (n=106), fatal (n=81), and not resolved (n=22).

Among the 87 cases with a fatal outcome, about 41% of the patients were aged ≥65 years. Four cases involved children. These fatal cases involved mainly females (64%). The daily dose in the fatal cases was most frequently >30 mg daily (<30 mg in 9 patients, 30 mg in 7 patients, and >30 mg in 47 patients). In 57 out of the 87 fatal cases a cardiovascular cause of death or sudden death was reported. Among these 57 cases, it should be pointed out that 43 cases were excluded from further

review mainly due to patients who had risk factors (n=27), implausible temporal relationship (n=8), alternative etiology (n=5) or insufficient information (n=3). The remaining 14 cases included 12 cases in which cause of death included cardiac arrhythmias (including ventricular arrhythmia, QT prolongation, Torsades de Pointes, and ventricular fibrillation), 1 case of cardiac and respiratory arrest, and 1 case of atrioventricular block. Of note, 11 of the 14 cases also had cardiovascular risk factors.

In addition, a second review (data lock point 31 January 2012) was conducted using the safety database of the originator with a focus on cardiac conduction events. Among the 156 cases retrieved (some of which had already been included in the first review), in 60 cases involving patients 12 years of age or older the daily dose was reported, and in approximately one third of these 60 cases the daily dose exceeded 30 mg. In 60 cases information on time to onset is provided, in 20 of these cases the event occurred on the same day of the first dose and in 44 cases the event occurred during the first week. Of the 156 cases, 97 cases reported co-suspect/concomitant medication use, and 33 cases had a fatal outcome (7 of which had already been identified in the first review). Six of these cases involved children.

Data on case reports received by other MAHs was also reviewed and did not raise additional issues.

In addition, an analysis of Eudravigilance data was performed and 219 cases were retrieved (data lock point 7 March 2013). The distribution by age group was as follows:

**Table 5 Eudravigilance analysis – distribution per age group of cases**

| Age Group | Number of cases |
|---|---|
| 0-9 years | 23 |
| 10-19 years | 12 |
| 20-29 years | 7 |
| 30-39 years | 22 |
| 40-49 years | 19 |
| 50-59 years | 28 |
| 60-69 years | 38 |
| 70-79 years | 25 |
| 80-89 years | 23 |
| 90-99 years | 4 |
| Unknown | 19 |

The median duration of treatment was 1.5 days (range: 0 – 333 days). It was not possible to calculate averages of the daily dose due to different routes of administration involved with different formats of dose reporting. The median time to onset was 2 days (range: 0 – 1135 days).

Among the 937 terms reported in total, the most frequently reported PTs were Dyspnoea (n=45), followed by Electrocardiogram QT prolonged (n=43), Torsade de pointes (n=29), Tachycardia (n=21), Arrhythmia (n=17), Dizziness (n=17), Drug interaction (n=17), Hypotension (n=17), Hypokalaemia (n=15), Bradycardia (n=14), Palpitations (n=14), Cardiac arrest (n=13), Fatigue (n=13), Chest discomfort (n=12), Cyanosis (n=12) Nausea (n=12), Syncope (n=10), Chest pain (n=9), Myocardial infarction (n=9), Pyrexia (n=9).

The most frequently reported grouped reactions (HLT) were Ventricular arrhythmias and cardiac arrest (n=64), followed by Rate and rhythm disorders NEC (n=60), and Breathing abnormalities (n=55). A total of 44 cases had medical history of cardiac problems.

It is noted that out of the cases identified in Eudravigilance, 24 referred to gastro-oesophageal reflux disease as the therapeutic indication.

***Pharmacoepidemiological studies***

Several epidemiological studies[7,8,9,10,11,12,13,14] provide estimates of the association between domperidone exposure and an increased risk of cardiac events. Except for one study, which found no cases exposed to either domperidone or the comparator, all the epidemiological studies suggest domperidone exposure was associated with an increased risk ratio for sudden cardiac death (SCD) and/or sudden ventricular arrhythmia (SVA).

A more recent and still unpublished company-sponsored pharmacoepidemiological study investigating the risk of out-of-hospital sudden cardiac death in users of domperidone, users of PPIs and users of metoclopramide was also assessed. The study design was an observational population-based case control study nested in a cohort of users of gastrointestinal medications. Patients with prescriptions of PPI or metoclopramide were selected as comparators in order to decrease the potential impact of confounding by indication. Controls were matched to cases by sex, age, and practice. A case-crossover analysis was also performed as a main sensitivity analysis in order to take into account the effect of unmeasured time-invariant potential confounders. Relevant databases were used as data sources. A total of 3,444 final cases of SCD were identified; 3,397 cases were included in the case-control analysis. A moderate statistically significant association was detected between current use of domperidone and SCD when compared with non-use of study medications (AOR = 2.09; 95% CI, 1.16-3.74). The case-crossover analysis showed a higher AOR (3.33; 1.87-5.92) substantiating the hypothesis that the risk of SCD increases with current use of domperidone when compared to non-use. The risk of SCD with current use of domperidone compared to non-use seems to increase with age (highest AOR in the age group 61-75 years) (4.15; 1.19 -14.48). The increased risk is especially observed with doses higher than 30 mg and patients aged 61-75 years. However, because of lack of power, an increased risk of SCD in subjects aged 60 years or younger and for doses <= 30 mg cannot be ruled out.

While it is agreed that all epidemiological studies have limitations, several studies (Van Noord, Johannes, Navarro) point to a higher risk in patients older than 60 years of age and/or taking daily doses above 30 mg.

***Conclusions on safety***

While the results of the thorough QT study on domperidone indicate that it does not significantly prolong the QTc interval when administered to healthy subjects at 10mg and 20mg qid, the concentration-QTc analysis has limited value and does not allow to accurately predict the effect on subjects where higher plasma concentrations can be reached e.g. due to drug-drug interactions or functional impairment.

A review of the safety database of the originator highlighted the high frequency of associated cardiovascular risk factors, cardiovascular history, and concomitant medications associated with cardiac arrhythmias in the patients concerned. A significant number of cases have been reported with concomitant or co-suspect medication known to prolong QT interval, CYP3A4 inhibitors, and/or

[7] Straus S. et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death European Heart Journal (2005) 26, 2007–2012.
[8] De Bruin et al. In-hospital cardiac arrest is associated with the use of non-antiarrhythmic QTc-prolonging drugs. Br J Clin Pharmacol 2006;63(2):216-23.
[9] Garcia-Rodriguez. Final report on the risk of ventricular arrhythmias and sudden death associated with gastric motility agents in the general population. Report to Johnson & Johnson, 1999.
[10] Garcia-Rodriguez. Final report on the risk of ventricular arrhythmias and sudden death associated with gastric motility agents in the diabetic population. Report to Johnson & Johnson, 1999
[11] Sturkenboom. Ventricular arrhythmia and sudden unexpected death and domperidone. Report to Johnson & Johnson, 2008 (based on the Van Noord study).
[12] Van Noord et al. Domperidone and ventricular arrhythmia or sudden cardiac death. Drug Safety 2010:33(11):1003-14.
[13] Jolly et al. Sudden death in patients receiving drugs tending to prolong the QT interval. Br J Clin Pharmacol 2009;68(5):743-51.
[14] Johannes et al. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepi Drug Saf 2010;19(9):881-88.

potassium–wasting diuretics. This is in line with the data coming from drug-drug interaction studies, and from spontaneous reporting. It is therefore important to ensure that appropriate risk minimisation measures are included in the product information to address this issue.

Cases involved all age groups including children, and a higher number of cases seem to be reported in the younger age groups (up to 5 years) than in older children. This is likely to be a reflection of the higher use in the younger age groups as well as the fact that these younger patients are usually more closely monitored.

Except for one study which found no cases exposed to either domperidone or the comparator, all the epidemiological studies suggest domperidone exposure was associated with an increased risk ratio for SCD and/or SVA. In some of the studies, particularly the Navarro study, a higher risk has been observed in patients over 60 years of age and/or those taking higher doses (over 30 mg/day).

Overall, based on clinical and non-clinical data it can be concluded that domperidone has the potential to induce QT-prolongation and that patients over the age of 60 years, taking daily doses >30 mg, with cardiac predisposition and/or who are co-administered other QT prolonging drugs or potent CYP3A4 inhibitors are at particularly increased risk.

Off-label use of domperidone is known to exist in certain indications. The overall safety profile of domperidone, and in particular its cardiovascular risk, should be taken into consideration..

## 2.2.3. Efficacy

***Domperidone in relief of symptoms of nausea and vomiting***

The efficacy of domperidone for improving the symptoms of nausea and vomiting has been studied in a wide variety of patient populations, including chemotherapy patients, patients with Parkinson's disease who are taking dopamine agonists, patients taking other medications or undergoing radiotherapy, post-operative patients and patients with CNS disorders including migraine, motion sickness or psychiatric illness. Domperidone was also studied in patients when the cause for symptoms was not clear.

*Nausea and vomiting induced by chemotherapy*

Nausea and vomiting may be acute, delayed or anticipatory; underlying mechanisms may (acute) or may not (delayed and anticipatory) be mediated by serotonin. While the mainstay of antiemetic therapy has been 5-hydroxytryptamine (5-HT3) antagonists, the antidopaminergic effect of domperidone forms a rationale for its use.

One small trial in adults demonstrated a large, clinically relevant treatment effect of domperidone, 20 mg tid, in the suppression of delayed nausea and vomiting in patients who had received highly emetogenic chemotherapy and had attained total suppression of acute emesis by ondansetron with or without dexamethasone. It remains unclear whether a daily dose of 40 mg domperidone is equally efficacious. In contrast, the quality of the studies and the reported effect sizes (versus an active comparator) in support of domperidone treatment starting before chemotherapy is low.

In the paediatric population, in contrast to the single double-blind, placebo controlled trial presented, which was prematurely ended, at least two comparator-controlled studies do add some evidence in support of the efficacy of domperidone in the treatment of nausea in the paediatric population at doses lower than 40 mg daily. However, in all studies an intravenous formulation of domperidone was used, which is no longer available. In conclusion, there is insufficient evidence from placebo-controlled, double blind randomised trials in support of an efficacy claim for the treatment of nausea and vomiting induced by chemotherapy in paediatric patients at a daily dose of 40 mg domperidone.

*Nausea and vomiting induced by anti-Parkinsonism medication in adults*

Anti-Parkinsonism medications can cause nausea and vomiting by stimulating the chemoreceptor trigger zone or by acting within the GI tract to promote gastric relaxation and delayed gastric emptying. The dopamine antagonist activity of domperidone, with its poor CNS penetration, provides a rational for its use in patients with nausea and vomiting due to anti-Parkinsonism medications.

Stocchi (n=128) performed a study to determine if prophylactic domperidone would allow for faster ropinirole (a dopamine agonist) titration. Two groups (fast groups) were titrated to ropinirole 7.5 mg/day over 21 days with concomitant oral domperidone 10 mg tid (53 patients) or placebo (24 patients); the other group (slow group) was titrated to ropinirole 7.5 mg/day over 42 days with matched placebo (51 patients). The study did not reach its primary efficacy endpoint which was related to the incidence of nausea during the 42-day titration period. Evidence in support of the efficacy of domperidone in the treatment of nausea and vomiting due to anti-Parkinsonism in adults at daily doses of 40 mg or lower is limited.

*Nausea and vomiting due to other medications or radiotherapy in adults*

Considering that the evidence in support of the efficacy of domperidone treatment of nausea and vomiting due to other medications or radiotherapy in adults is generated in four open label, uncontrolled trials including very low patient numbers, the level of evidence is both qualitatively and quantitatively considered to be insufficient to support the indication.

*Post-operative nausea and vomiting in adults*

Only one small, trial of acceptable quality demonstrates a statistically and clinically relevant effect of domperidone (60 mg suppository) in the treatment of post-operative nausea and vomiting in adults, in support of the proposed therapeutic indication. No efficacy data using a daily dose of 40 mg domperidone or less are available.

*Nausea and vomiting due to CNS disorders*

Altogether, some of the efficacy data presented for the treatment of nausea and vomiting in adults due to CNS disorders such as migraine and motion sickness suggest that domperidone (20 mg to 30 mg) has some effect in these conditions, however methodological flaws and plain trial outcomes impair either a full appreciation of the study results or are not in support of the indication.

Only a single study was provided investigating the effect of domperidone at a daily dose <40 mg in the treatment of nausea and vomiting in confirmed common migraine in paediatric patients. The study was not blinded, and domperidone treatment was continuous for a period of 8 weeks.

Most of the studies presented in support of a general indication in nausea and vomiting indication were conducted with a daily dose of 60 mg, and in some cases even higher. When targeting the 30 mg/day dose for adults which was found to be associated with a lower risk, the more relevant studies are described below.

**Table 6 Adult patients: efficacy in nausea and vomiting – main studies supportive of the efficacy of a posology of 10 mg three times a day**

| Author | Study Design | Diagnosis No. of Patients (Evaluated) Age | Entry Criteria | Assessment Method | Dose and Duration; Concomitant Medication (CM) | Nausea / Vomiting Results >better than (p<0.05); '=' difference not significant |
|---|---|---|---|---|---|---|
| **Placebo-controlled (continued)** | | | | | | |
| De Loose F, 1980[11] LMD21025 | DB-PG-PC | Chronic postprandial gastrointestinal distress<br><br>n=281<br>Median 43 yrs (17-92)<br><br>D: n=NS (141)<br>P: n=NS (140)<br><br>No organic disease in 132 (61 D, 71 P); Others: hiatus hernia (17), esophageal (22), gastric (132) or biliary (41) disorders | ≥1 of 5 target symptoms with score ≥2 | A: 4-point symptom score (0-3)<br><br>B: global evaluation<br><br>C: assessment symptom clusters vs underlying disease | D 10 mg TID<br>P TID<br>for 4 wks<br><br>CM: GI medications discontinued 1 wk prior to study | Baseline incidence:<br>Postprandial nausea D=77.3%; P=72.1%<br>Postprandial vomiting D=51.1%; P=50.0%<br><br>Week 2 incidence<br>Postprandial nausea D=48.2%; P=66.4% (p<0.001)<br>Postprandial vomiting D=22.7%; P=43.6% (p<0.001)<br><br>Week 4 incidence<br>Postprandial nausea D=31.9%; P=65.7% (p<0.001)<br>Postprandial vomiting D=10.6%; P=40.7% (p<0.001)<br><br>Median percentage change from baseline in postprandial nausea and vomiting cluster score<br>Week 2 D=-66.7%; P=0.0% (p<0.001)<br>Week 4 D=-100.0%; P=-18.3% (p<0.001) |
| Englert W, 1979[14] LMD13791 | DB-CO-PC | Chronic postprandial dyspepsia<br><br>D=P: n=48 (48)<br>Mean 32 yrs (17-53)<br><br>Chronic gastritis (13), nervous gastritis (21), duodenal/gastric ulcer (7/2), various (6) – 1 pt with 2 diagnoses | ≥5 of 9 target symptoms | 4-point symptom score (0-3) | D 10 mg TID<br>P TID<br>for 4 wks<br><br>CM: NS | Baseline incidence<br>Nausea D=P=26/48<br>Vomiting D=P=18/48<br><br>Week 4 incidence<br>Nausea D=6/48; P=20/48 (p<0.001)<br>Vomiting D=3/48; P=15/48 (p=0.002)<br><br>Change from baseline<br>Nausea D=p<0.001; P=nsd<br>Vomiting D= p<0.001; P=nsd |

| Author | Study Design | Diagnosis No. of Patients (Evaluated) Age | Entry Criteria | Assessment Method | Dose and Duration; Concomitant Medication (CM) | Nausea / Vomiting Results >better than (p<0.05); '=' difference not significant |
|---|---|---|---|---|---|---|
| **Placebo-controlled (continued)** | | | | | | |
| Von Matushka, 1979[32] LMD18089 | DB-PG-PC | Postprandial dyspepsia<br><br>n=166 (123)<br><br>D: n=62 (62)<br>Mean 42.4 yrs<br><br>P: n=61 (61)<br>Mean 42.7 yrs | ≥3 of 9 target symptoms with severity score ≥2 | A: 4-point symptom score (0-3)<br><br>B: global evaluation<br><br>C: comparison vs previous medication | D 10 mg TID<br>P TID<br>for 4 wks<br><br>CM: anticholinergics, antiemetics, prokinetics stopped 1 wk before study start; AA and minor tranquillizers allowed to continue | Week 2 reduction in nausea score D>P (p<0.01)<br><br>Week 4 reduction in nausea score D>P (p<0.05)<br><br>Week 4 change from baseline<br>D= p<0.001; P=nsd |

The study data from De Loose[15], Englert[16] and Von Matushka[17] support the use of domperidone 10 mg tid in the suppression of nausea and vomiting symptoms at week 2 and/or week 4 of treatment. In these studies, 251 and 249 patients received domperidone and placebo, respectively. Clinically relevant improvement in nausea and/or vomiting scores were reported in these studies following domperidone treatment compared to placebo.

For the paediatric population, limited data exists in support of the efficacy in nausea and vomiting. The studies submitted in support of paediatric use have methodological limitations (Clara 1979, De Loore, 1979 and Hegar, 2009) such as inconsistency in outcome (e.g. demonstrating superiority over placebo for vomiting but not for nausea symptoms), small number of patients or inclusion of patients with other conditions. The daily doses in these studies varied between 0.8 mg/kg/day and 0.9 mg/kg/day.

***Domperidone in dyspeptic symptoms***

[15] 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.
[16] 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.
[17] 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.

Dyspepsia is a disorder recognised in clinical practice as a complex of symptoms that originate in the upper gastrointestinal tract. The symptoms include upper abdominal pain or discomfort, early satiety, fullness, bloating in the upper abdomen, nausea and retching. Not all dyspepsia symptoms will be present in every patient, and symptoms are usually of waxing and waning nature. Functional dyspepsia is a chronic condition requires long-term treatment.

A number of studies were submitted in support of the efficacy of domperidone in this indication. Findings were not always consistent and, when positive, were modest. However all of the studies had methodological issues such as diagnosis, entry criteria, low number of patients included, small trial duration, evaluation criteria and outcome assessment which limit the ability to draw conclusions on the efficacy of the product. Six meta-analyses in this indication were assessed, but the outcomes are also affected by the methodological flaws of the trials included.

***Domperidone/cinnarizine for motion sickness***

Three small placebo-controlled double blind studies were submitted in support of the above indication, including a total of 90 patients of which 48 were treated with the combination and evaluated for efficacy. In the Doweck study[18], no significant effects were reported. The Oosterveld (1987)[19] study demonstrated a significant effect of the combination therapy on duration and amplitude of nystagmus. However the doses used were higher than the currently approved (30 mg domperidone, 40 mg cinnarizine, a combination of both or placebo). In the Oosterveld (1979)[20] study, the 10 patients included had significant reductions of nystagmus duration with the active medications (domperidone 20 mg, cinnarizine 75 mg or cinnarizine/domperidone 75mg/10mg). During the 6-hour sessions, the combination therapy was significantly better than cinnarizine monotherapy at only one timepoint.

***Other uses of domperidone***

Data was also assessed in relation to the use of domperidone in conditions such as GERD, gastroparesis and insufficient lactation. Gastroparesis and insufficient lactation are not approved indication for domperidone in the European Union and therefore the efficacy in these indications is not discussed in this report.

GERD is defined as persistent reflux that occurs more than twice a week. The overall evidence in support of the indication is limited. Of the placebo controlled, double blind studies presented, domperidone was usually used at a dose between 60 and 120 mg, the number of patients was low and the results were inconsistent between studies after 4 weeks of treatment.

***Conclusions on efficacy***

Overall there is sufficient evidence in support of the use of domperidone 10 mg up 3 times a day in a general indication of treatment of nausea and vomiting in adults. The data in support of the paediatric use in this indication is limited, however the mechanism of action is not expected to differ between adults and children. It would nevertheless be important to generate further data to document the efficacy in the paediatric population.

Data in support of other indications are extremely limited. In particular regarding dyspepsia and GERD, there is limited data in support of the long-term efficacy of domperidone.

[18] Doweck I, Gordon CR, Spitzer O, Melamed Y, Shupak A. The vestibulo-oculur reflex (VOR) under the influence of cinnarizine. J Vestib Res. 1994;4(3):215-220.
[19] Oosterveld WJ. The combined effect of cinnarizine and domperidone on vestibular susceptibility. Aviat Space Environ Med. 1987;58:218-223.
[20] Clinical Research Report [Oosterveld WJ] RA33 812/43/RA516/Domperidone/Cinnarizine. The combined effect of domperidone and cinnarizine on vestibular nystagmus. Janssen Research Products Information Service. Unpublished internal report. Jan 1979.

## 2.3. Risk minimisation activities

The PRAC agreed that all Market Authorisation Holders of domperidone-containing medicinal products shall submit a Risk Management Plan (RMP) to the National Competent Authorities after the finalisation of the procedure. The key elements of this RMP are described below:

| ***Part II - Safety specification*** | |
|---|---|
| Potential for off-label use in: | stimulation of lactation in breastfeeding women |
| | gastroesophageal reflux disease |
| | diabetic and non-diabetic gastroparesis |
| | symptoms of postural hypotension in patients with Parkinson's disease |
| Important identified risks: | cardiac events (QTc prolongation, Torsades de Pointes, serious ventricular arrhythmia, sudden cardiac death |
| | Off label use (see above) |

| ***Part III - Pharmacovigilance plan*** | | |
|---|---|---|
| *Areas requiring confirmation or futher investigation* | *Proposed routine and additional PhV activities* | *Objectives* |
| Safety concern 1: Risk of cardiac events | | |
| To collect and monitor the cardiac events (expected and unexpected) | Routine pharmacovigilance activities will be conducted, including review of incoming case reports, aggregate safety data and review of the medical literature and targeted surveillance of key events. | To collect any cardiac events. To identify any signal indicating unexpected occurrence of cardiac events |
| Safety concern 2: Off-label use | | |
| To monitor, estimate and study the occurrence of off-label use | Routine pharmacovigilance activities will be conducted, including review of incoming case reports, aggregate safety data and review of the medical literature and targeted surveillance of key events. | To identify any signal indicating unexpected occurrence of off-label use |

**Imposed mandatory additional pharmacovigilance activity (key to benefit-risk balance):**

A drug utilisation study to assess the effectiveness of risk minimisation measures and to monitor off-label use.

| ***Part V – Risk minimisation measures*** |
|---|

| *Part V – Risk minimisation measures* | |
|---|---|
| **Safety concern** | **Cardiac events (QTc prolongation, Torsade de Pointes, serious ventricular, arrhythmia, sudden cardiac deaths)** |
| Objective(s) of the risk minimisation measures | Provide information regarding the risk of cardiac events and reduce their frequency |
| Routine risk minimisation measures | Text in the SmPC and PL including dose reduction, precautionary information in the product information |
| Additional risk minimisation measure(s)<br>(repeat as necessary) | Safety reviews in PSURs<br>Distribution of a DHPC |
| **Safety concern** | **Off-label use** (e.g. stimulation of lactation in breast feeding women, gastroesophageal reflux disease, diabetic and non-diabetic gastroparesis, symptoms of postural hypotension in patients with Parkinson's disease) |
| Objective(s) of the risk minimisation measures | To monitor, estimate and study the occurrence of off-label use in order to reduce the frequency of off-label use |
| Routine risk minimisation measures | Safety reviews in PSURs |

In order to ensure that paediatric patients receive the correct dose adjusted per body weight, oral liquid formulations are to be supplied with an appropriate measuring device.

In accordance also with the Article 23 of Regulation (EC) No 726/2004 the products will be included in the list of products for additional monitoring. The relevant information as well as the pictogram (triangle) will be added in the product information of the products.

## *2.4. Product information*

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the potential cardiovascular risks associated with domperidone use. These changes include amendments to sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics.

Importantly there is a restriction of the use of oral formulations of domperidone only for the relief of the symptoms of nausea and vomiting in adults, and in children (only where the paediatric indication is already approved). In addition these products should be used at the lowest effective doses necessary to control nausea and vomiting and for the shortest duration possible which usually does not exceed one week.

In addition, the PRAC considered that domperidone use should be contraindicated in patients with:

- moderate or severe hepatic impairment

- patients with known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases
- co-administration of all QT-interval prolonging drugs
- co-administration with potent CYP3A4 inhibitors

Further warnings and precautions of use relating to the cardiovascular effects of domperidone were also included and other important information harmonised.

The corresponding sections of the package leaflet were amended accordingly.

# 3. Overall discussion and benefit / risk assessment

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

The PRAC noted that there are apomorphine products approved in Europe and used in Parkinson's disease for which the product information makes reference to use of domperidone to prevent digestive disorders and orthostatic hypotension. It was noted that the dose and treatment duration of domperidone for this indication differs from the ones considered within the framework of the current referral procedure. Nevertheless, the PRAC noted that apomorphine is itself a QT-prolonging drug.

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 the potential benefits are considered to be outweighed by the identified cardiac risk.

The available 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.

While it is recognised that healthcare systems differ from Member State to Member State, the PRAC noted that given the new recommendations medical intervention is likely to be needed to identify patients suitable for treatment with 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 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. Wherever 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 in certain indications. The overall safety profile of domperidone, and in particular its cardiovascular risk, should be taken into consideration.

# 4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to raise awareness of the new recommendations in the product information and other risk minimisation measures. The specialists targeted are general practitioners, gastroenterologists, paediatricians (in Member States where there is a paediatric indication) and pharmacists. The communication is to be sent in accordance with the agreed communication plan. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachment to this report).

# 5. Conclusion and grounds for the recommendation

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 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 Committee, 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.

# Appendix 1

## Divergent positions to PRAC recommendation

## *Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data*

Procedure No: EMEA/H/A-31/1365

Domperidone containing medicinal products

## Divergent position

We, the undersigned

Agree that the proposed minimisation risk measures are sufficient to ensure a favourable benefit-risk ratio in adults.

However, we stand against its use in the paediatric population under 12 years of age and adolescents weighing less than 35 kg. This position is based on the potential risk and the insufficiency of available data in children, where the efficacy relies on a long-lasting experience associated with an extrapolation of adult population data. At the new proposed doses the effectiveness is not established and the cardiac risk is not excluded.

In addition, the misuse in children, especially in infants, is a major issue which could be definitively avoided by a contra-indication. Indeed, the medical need for this product in the treatment of acute nausea and vomiting in children has not been clearly established.

**PRAC members expressing a divergent position:**

| | | |
|---|---|---|
| Carmela Macchiarulo (IT) | 6 March 2014 | Signature: ……... |
| Isabelle Robine (FR) | 6 March 2014 | Signature: ……... |
| Marco Greco | 6 March 2014 | Signature: ……... |