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## Assessment report

Metoclopramide only containing medicinal products

International Non-proprietary Name: metoclopramide

**Procedure number:** EMEA/H/A-31/1321

**Referral under Article 31 of Directive 2001/83/EC**

### Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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# 1. Background information on the procedure

## 1.1. Referral of the matter to the CHMP

On 7 December 2011, France triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing metoclopramide should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

## 2. Scientific discussion

### 2.1. Introduction

Metoclopramide is a substituted benzamide used for its prokinetic and antiemetic properties. It possesses parasympathomimetic activity as well as being a dopamine-receptor (D2) antagonist with a direct effect on the chemoreceptor trigger zone. It also has serotonin-receptor (5-HT<sub>3</sub>) antagonist properties.

Metoclopramide has been authorised in the European Union since the 1960's and marketing authorisations currently exist in all Member States as well as in Norway and Iceland. It is available in a variety of pharmaceutical forms (e.g. tablet, prolonged-release tablet, oral solution, suppository, solution for injection). Combination products are also approved, but this procedure focused on the assessment of the monocomponent products.

The authorised indications for products are different but can broadly be grouped in the following way:

- Chemotherapy or radiotherapy induced nausea and vomiting (CINV or RINV)
- Post-operative nausea and vomiting (PONV)
- Nausea and vomiting associated with migraine
- Nausea and vomiting of other origins
- Gastrointestinal motility disorders including gastroparesis
- Gastroesophageal reflux disease (GORD) and dyspepsia
- Adjuvant to surgical and radiological procedures

Each individual product is authorised for one or more of these indications, and in some cases the indication is specific to adults and/or children. There is no clear correlation between formulations and indications.

Metoclopramide crosses the blood-brain barrier and is associated to extrapyramidal disorders and other serious neurological adverse events, which are of particular concern in children.

In addition to the neurological risk, there is also a risk of occurrence of cardiovascular adverse events including rare but potentially serious reactions such as bradycardia, atrioventricular block, cardiac arrest, mainly with the formulations for intravenous use.

A paediatric worksharing procedure under Article 45 of Regulation (EC) No 1901/2006<sup>1</sup> to assess information from paediatric studies with metoclopramide has been concluded in 2010 with a

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<sup>1</sup> *Rapporteur's public paediatric assessment report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No. 1901/2006, on Primperan (and others) / Metoclopramide (DE/W/007/pdWS/001)*, (2010). Retrieved from [http://www.hma.eu/fileadmin/dateien/Human\\_Medicines/CMD\\_h\\_/Paediatric\\_Regulation/Assessment\\_Reports/Article\\_45\\_work-sharing/Metoclopramid\\_Art.45\\_PdAR\\_Update.pdf](http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Metoclopramid_Art.45_PdAR_Update.pdf)

recommendation that Member States should introduce the following changes to the product information:

- Contraindication in neonates;
- Only the intravenous formulations remain approved for use in paediatric patients >1 year of age, and only for the indication 'treatment of postoperative nausea and vomiting';
- Inclusion of specific warnings and precautions, mainly regarding the extrapyramidal adverse events.

After finalisation of the procedure under Article 45 of Regulation (EC) No 1901/2006, the Marketing Authorisation Committee of the French Competent Authority performed a national assessment of the benefit-risk balance of metoclopramide in children and decided, in October 2011, to extend the contraindication to all children under 18 years old for all formulations. This was based on insufficient evidence of efficacy in children in the concerned indications and on the safety issue of neurological symptoms.

Based on the risk of neurological and cardiovascular adverse events, as well as on the limited evidence of efficacy for all indications approved, the French Competent Authority triggered a referral under Article 31 of Directive 2001/83/EC and asked the CHMP to review the benefit-risk balance of metoclopramide-containing products in all populations, particularly in children and the elderly. The French Competent Authority considered it particularly important that the therapeutic indications and safety information be made consistent across Member States.

Overall patient exposure to metoclopramide is difficult to estimate due to the high number of products, formulations and indications. Estimates based only on data provided by the brand leader indicate that, during the period between October 1999 and September 2011, exposure corresponded to 1.92 billion treatment days.

## **2.2. Clinical efficacy**

For each one of the indications approved, MAHs submitted available evidence of efficacy, including clinical trials, meta-analyses and reviews. The most relevant data for each indication is summarised and discussed below. Data for adults is presented separately from data on children. No specific efficacy data on the elderly were submitted.

### **2.2.1. Results**

#### **2.2.1.1. Chemotherapy induced nausea and vomiting (CINV)**

CINV is an adverse effect associated with most chemotherapy drugs and regimes. It can be divided in:

- Acute (occurring within 24 hours of chemotherapy)
- Delayed (occurring more than 24 hours after chemotherapy)

Chemotherapy is associated with nausea and vomiting in 70-80% of patients, depending on the emetogenic potential of the chemotherapy regimen. Patient-related risk factors for CINV include age, female gender and history of CINV, motion sickness or nausea and vomiting during pregnancy.

#### Meta-analyses and reviews

##### *Acute CINV*

Jantunen *et al.* (1997) reviewed the randomised studies published until April 1996 comparing 5-HT<sub>3</sub> receptor antagonists with the conventional anti-emetics in the prophylaxis of acute CINV.

Fifteen (15) randomised trials compared 5-HT<sub>3</sub> antagonists to high-dose metoclopramide treatments after cisplatin chemotherapy (highly emetogenic). The percentage of patients responding to anti-emetic prophylaxis varied greatly from trial to trial; overall 49% of patients treated with metoclopramide were free from vomiting during acute phase, compared to 61% for patients receiving 5-HT<sub>3</sub> receptor antagonists alone or with dexamethasone. Overall, the meta-analysis showed that 5-HT<sub>3</sub> antagonists reduced the risk of acute vomiting in comparison to conventional anti-emetics in patients receiving highly emetogenic chemotherapy; the odds ratios varied from 0.22 to 1.03, resulting in a combined odds ratio of 0.60 (95% CI 0.51-0.70).

Eleven (11) trials compared conventional antiemetics (most commonly low dose [20-80mg] metoclopramide) to 5-HT<sub>3</sub> receptor antagonists in moderately emetogenic chemotherapy. The percentage of patients responding to anti-emetic prophylaxis varied greatly from trial to trial; overall 51% (range 22-89%) of patients treated with conventional antiemetics were free from vomiting during acute phase, compared to 68% (range 45-82%) for patients receiving 5-HT<sub>3</sub> receptor antagonists. Overall, the meta-analysis showed that 5-HT<sub>3</sub> receptor antagonists reduced the risk of acute vomiting in comparison to conventional anti-emetics in patients receiving moderately emetogenic chemotherapy; the odds ratio of vomiting in each trial varied from 0.20 to 1.69 resulting in combined odds ratio of 0.47 (95% CI 0.39-0.58).

#### *Delayed CINV*

Jordan *et al* (2009) conducted a meta-analysis of six trials (n=700) comparing 5-HT<sub>3</sub> receptor antagonists and metoclopramide in the prevention of delayed emesis in moderately emetogenic chemotherapy and demonstrated no apparent difference in efficacy. However, the results of this meta-analysis have to be interpreted with caution due to the potential carry over effect from the acute phase and heterogeneity of the included studies.

#### Clinical studies

To support this indication, a number of clinical studies were identified. The 14 more recent randomised studies included more than 2200 patients. Thirteen (13) of these studies included metoclopramide as a comparator in evaluating a 5-HT<sub>3</sub> receptor antagonists, the other was a placebo-controlled trial which assessed the efficacy of metoclopramide added to ondansetron and dexamethasone.

Four (4) of these studies were in female patients only; in total 54% of the patients included were females. Overall, the age range of patients included was 18-90 years. Administration regimens covered a large range of doses, from 10 to 40 mg, or from 1 to 7 mg/kg for the IV formulation, and from 15 to 120 mg/day or 2 mg/kg/day for the oral formulation. The rectal form was administered as 20 mg as required.

In acute CINV, 5-HT<sub>3</sub> receptor antagonists resulted in 47 to 97% complete control, versus 16 to 85% for metoclopramide.

In delayed CINV, 33 to 96% of complete control was achieved with 5-HT<sub>3</sub> receptor antagonists versus 30 to 85% with metoclopramide.

In six studies a statistically significant difference in favour of 5-HT<sub>3</sub> receptor antagonists was observed, and most studies concluded in favour of 5-HT<sub>3</sub> receptor antagonists. Some studies concluded in favour of metoclopramide, particularly for delayed CINV.

### 2.2.1.2. Radiotherapy induced nausea and vomiting (RINV)

RINV is associated with some courses of radiotherapy, and the risk of RINV depends on the part of the body being treated, the dose of radiation given and the frequency of treatment. A combination of radiotherapy with chemotherapy increases the risk of nausea and vomiting.

#### Meta-analyses and reviews

Salvo *et al.* (2012) reviewed 9 randomised trials in prophylaxis of RINV, where 5-HT<sub>3</sub> receptor antagonists were used as comparator. Given a significant degree of clinical heterogeneity between the trials, the authors conducted separate meta-analyses for the three following comparisons: 5-HT<sub>3</sub> receptor antagonists versus placebo, tropisetron versus metoclopramide (3 studies) and general 5-HT<sub>3</sub> receptor antagonists versus metoclopramide (3 studies with tropisetron + 1 with ondansetron).

Pooled results of complete control of acute emesis showed a significant benefit of tropisetron over metoclopramide (n=109; RR 0.36, 95% CI 0.18-0.71). With the addition of one study which investigated ondansetron 8mg versus metoclopramide 10mg three times daily for 3-5 days, the effect size was more profound (n=214; RR 0.27, 95% CI 0.15-0.47).

#### Clinical studies

Mystakidou *et al.* (2010) conducted a retrospective open label study to evaluate the optimum prophylactic treatment for RINV in 576 patients. Patients were allocated in 5 treatment groups: 120 tropisetron, 129 tropisetron + dexamethasone, 101 metoclopramide, 119 dexamethasone and 107 metoclopramide + dexamethasone. To determine the optimum antiemetic prophylactic treatment, nausea and vomiting were evaluated at baseline, 24 and 72 h after the initiation of radiotherapy, and at the end of every week during radiotherapy. Patients receiving prophylactic antiemetic treatment with tropisetron + dexamethasone had significantly reduced odds for nausea and vomiting, and significantly less severe nausea and vomiting than any other treatment group.

### 2.2.1.3. Post-operative nausea and vomiting (PONV)

Post-operative nausea and vomiting may occur in up to 80% of patients post-operatively, particularly following prolonged abdominal or gynaecological surgery, although many studies estimate the incidence to be lower. Risk factors for the development of PONV include young age, female gender and history of PONV or motion sickness. Anaesthesia and drugs used during surgery may also contribute to the risk.

#### Meta-analyses and reviews

A Cochrane review conducted by Carlisle *et al.* (2006) included 737 studies (n=103 237) and investigated the effects of 60 different drugs and 4 outcomes: nausea, vomiting, nausea and vomiting and rescue therapy. The patients were distributed as follows: 76% female and 24% male, 78% adults and 22% children. Nine drugs had an effect on all 4 outcomes: cyclizine, dexamethasone, 5-HT<sub>3</sub> receptor antagonists (dolasetron, granisetron, ondansetron, ramosetron and tropisetron), droperidol and metoclopramide. Metoclopramide was included in 158 studies, usually administered intravenously before surgery as a single dose from 0.1 to 0.5 mg/kg and from 10mg to 50mg. In most studies, a dose of 10mg metoclopramide by intravenous route was used. Results showed that in the 24-hour post-operative period, nausea and/or vomiting were reported in up to 61% of patients treated with metoclopramide, 47% of patients treated with 5-HT<sub>3</sub> receptor antagonists, 23% of patients treated with dexamethasone, 73% of patients treated with other drugs and 80% of patients treated with placebo. According to the authors, it is not possible to conclude whether these drugs differ in their ability to prevent PONV. There was no clear dose-response for metoclopramide in the studies reviewed.

### Clinical studies

A total of 22 randomised clinical studies were submitted, including more than 7800 patients. Twelve (12) of these were placebo-controlled.

In all the studies for prophylaxis of PONV, a single intravenous dose of metoclopramide was given ranging from 0.1-0.5 mg/kg in most studies. One study investigated 3 different doses and is described below. The conclusions of the studies were not consistent; some were in favour of metoclopramide as monotherapy or in combination with other agents including dexamethasone, while others were in favour of comparators including 5-HT<sub>3</sub> receptor antagonists, dexamethasone and droperidol.

Wallenborn *et al.* (2006) conducted a randomised double-blind trial in 3140 patients to determine whether a single intravenous dose of metoclopramide 10mg, 25mg or 50mg combined with 8mg dexamethasone and given 30-60 minutes before the end of surgery is more effective for the prevention of PONV than dexamethasone alone. The cumulative incidence of PONV was reduced from 23.1% (placebo + dexamethasone) to 20.6% (metoclopramide 10mg + dexamethasone), 17.2% (25mg) and 14.5% (50mg). The incidence of early (<12 hours after surgery) PONV was the same for the 25mg and 50mg doses. The incidence of late (>12 hours after surgery) PONV was lower for the 50mg dose.

#### **2.2.1.4. Nausea and vomiting associated with migraine**

Migraine is a common, disabling headache disorder associated with nausea and vomiting, photophobia and phonophobia.

### Meta-analyses and reviews

Cochrane reviews were conducted in 2010-2011 analysing the use of aspirin (Kirthi *et al.* 2010) and paracetamol (Derry *et al.* 2010) with or without an antiemetic for acute migraine headaches in adults. The addition of metoclopramide 10mg to aspirin 1000mg was found to significantly reduce nausea and vomiting associated with migraine, compared to aspirin 1000mg alone. The combination of paracetamol 1000mg and metoclopramide 10mg was found to provide similar relief of headache and sensitivity to light and noise compared to sumatriptan 100mg, but no conclusions were reached on nausea and vomiting.

A 2008 review by Azzopardi *et al.* (2008) compares the combination of oral metoclopramide plus an analgesic with oral triptan monotherapy in the treatment of migraine. In the studies reviewed, for all primary and secondary efficacy outcomes, including migraine-associated nausea and vomiting, sumatriptan and zolmitriptan were similar or superior to oral metoclopramide plus an analgesic.

Another review by Colman *et al.* (2004) assessed the evidence from controlled trials on the efficacy and tolerability of parenteral metoclopramide for acute migraine in adults. A total of 13 eligible trials totalling 655 patients were found. In studies comparing metoclopramide with placebo, metoclopramide was more likely to provide significant reduction in migraine pain (OR 2.84, 95% CI 1.05-7.68). Used as the only agent metoclopramide showed mixed effectiveness when compared to other agents. The authors concluded that metoclopramide is an effective treatment for migraine headache and may be effective when combined with other treatments.

Another meta-analysis by Gong *et al.* (2012) evaluated the curative effect of metoclopramide on treating migraine. A total of 16 randomised controlled trials were included, with 985 patients receiving metoclopramide treatment, 267 patients on placebo and 816 patients on other drugs. The authors concluded that the remission rate for metoclopramide was significantly higher than placebo, but not statistically different from the remission rate in patients on other drugs. However, the incidence of adverse reactions was significantly lower with metoclopramide than with other drugs on migraine.

### Clinical studies

A dose-finding study by Friedman *et al.* (2011) of intravenous metoclopramide in acute migraine, using doses of 10mg, 20mg and 40mg did not find a significant difference in pain relief at 1 hour and 48 hours post-dose. The authors conclude that 20mg or 40mg of metoclopramide is no better for acute migraine than 10mg of metoclopramide.

#### **2.2.1.5. Nausea and vomiting of other origins**

Data presented in support of this indication focused on different clinical settings such as: nausea and vomiting induced by opioids and nausea, vomiting of any aetiology in an emergency department, nausea during pregnancy, motion sickness. A small number of studies were submitted and results were not always consistent.

A study by Lu *et al.* (2010) concluded that, when added to postoperative patient-controlled morphine analgesia regimens, a combination of metoclopramide with diphenhydramine is more effective than either substance alone in reducing postoperative nausea and vomiting in patients treated with dexamethasone.

Another study by Rubio *et al.* (2011) included 22 patients and concluded that during ambulance transport in mountainous setting, the administration of metoclopramide is superior to both diphenhydramine and placebo in the treatment of motion sickness.

In the largest study submitted on nausea during pregnancy, Klauser *et al.* (2011) concluded that treatment with either metoclopramide or ondansetron resulted in significant improvement of nausea and vomiting in pregnancy, with half of women showing a reduction from severe symptoms to moderate or mild symptoms within 3 days of treatment initiation.

#### **2.2.1.6. Gastrointestinal motility disorders**

Delayed gastric emptying in the absence of mechanical obstruction is known as gastroparesis and may occur as a complication of autonomic neuropathy in diabetic patients, as a complication following gastric surgery or may be idiopathic. It causes symptoms such as bloating, nausea, abdominal pain, heartburn and weight loss, and can have significant impact on glycaemic control in diabetic patients.

### Meta-analyses and reviews

As part of the UK National Institute for Clinical Excellence (NICE) clinical guideline 66 for type 2 diabetes, six studies investigating the use of domperidone, erythromycin and metoclopramide for the treatment of gastroparesis were reviewed. Oral metoclopramide (10mg 4 times daily) was found to significantly improve symptom score compared to placebo in 2 studies. No significant difference in the improvements in symptom score were identified in 2 studies that compared metoclopramide (10mg 3-4 times daily) with either domperidone or erythromycin.

A review was also conducted by Lee *et al.* (2010) which considered 5 controlled trials and four open label series. Symptoms improved in seven studies and gastric emptying was accelerated in five studies. The authors concluded that metoclopramide has been demonstrated to be effective for the short-term treatment of gastroparesis for up to three weeks, but long-term efficacy has not been proven.

In another review by Lata *et al.* (2003), three small randomised double blind studies were found assessing the effect of metoclopramide in diabetic gastroparesis in treatment duration over 3 weeks. The authors concluded that there was no consistent benefit from the use of metoclopramide for more

than 1 month, and therefore there is insufficient evidence to conclude on the long term efficacy of metoclopramide in diabetic gastroparesis.

A review by Gumaste *et al.* (2008) considered evidence for different pharmacological and non-pharmacological treatment options in gastroparesis. In relation to metoclopramide this review concludes that a minority of patients may experience symptom benefit from therapy. However, there appears to be poor correlation between the improvement in gastric emptying and reduction of symptoms. When compared with erythromycin, metoclopramide proved to be inferior in terms of symptom relief in one study. Other studies have shown that metoclopramide may be equally effective or marginally inferior to domperidone in efficacy. Patients may develop tolerance over time and uncomfortable side effects may limit its use in up to 30% of patients.

Another meta-analysis by Sturn *et al.* (1999) considers the relative potency of prokinetics in the management of gastroparesis. This review highlights the methodological limitations of the studies included, and therefore the conclusions that can be made. Poor correlation between improvements in gastric emptying and symptom relief were noted. The analysis suggests that metoclopramide is inferior to erythromycin or domperidone for this indication.

#### Clinical studies

A double-blind multicentre comparison trial performed by Patterson *et al.* (1999) included 93 patients and concluded that metoclopramide (10mg 4 times daily) was similarly effective to domperidone (20mg 4 times daily) in improving symptoms of diabetic gastroparesis. However central nervous system effects were more serious and more common with metoclopramide.

### **2.2.1.7. Gastroesophageal reflux disease and dyspepsia**

#### Meta-analyses and reviews

A review by Poe *et al.* (2003) evaluated the experience of 214 patients presenting with cough of at least 3 weeks duration. An anatomic diagnostic protocol was used to identify and treat those with reflux disease-related cough, and a therapeutic trial of a proton-pump inhibitor (PPI) with or without a prokinetic agent (10 mg of metoclopramide or cisapride 4 times daily) was used. A total of 56 patients were prescribed a PPI. The prokinetic agent was added if esophageal dysfunction was suspected or response was inadequate. Twenty-four (24) patients responded to PPI therapy and 18 patients responded when the prokinetic agent was added. The authors concluded that 4 to 6 weeks of a PPI alone or in combination with a prokinetic agent successfully diagnoses and treats four out of five patients with reflux-related cough.

A Cochrane review of pharmacological interventions for non-ulcer dyspepsia was conducted by Moayyedi *et al.* (2006). This review was meanwhile withdrawn and is being split into 4 different reviews, one of which will specifically review prokinetics for functional dyspepsia. The 2006 review concluded that prokinetics were significantly more effective than placebo based on 19 trials with dichotomous outcomes, but a funnel plot suggested that these results could be due to publications bias or other small study effects.

A further review of literature identified a systematic review (Van Prinxteren *et al.* 2000) that concludes that evidence for the use of prokinetics in gastroesophageal reflux disease is weak with little or no sustained effect on acid exposure or healing of oesophagitis.

#### Clinical studies

One MAH submitted an assessment of randomised trials evaluating metoclopramide in gastroesophageal reflux disease and dyspepsia but very few studies were identified and the efficacy data was considered to be very poor.

### **2.2.1.8. Adjuvant to surgical and radiological procedures**

This refers to the use of metoclopramide as an adjuvant in procedures to examine and investigate the gastrointestinal tract. It may include gastroscopy, capsule endoscopy and radio-labelled 'meals'.

#### Meta-analyses and reviews

Barkun *et al.* (2010) conducted a meta-analysis to review the use of prokinetics before gastroscopy in patients with acute upper gastrointestinal bleeding. The review concluded that the use of a prokinetic significantly reduced the need to repeat the gastroscopy, but did not improve other clinically relevant measurable outcomes. Subgroup analysis suggested that the beneficial effects were associated with the use of erythromycin, but not metoclopramide because of very small patient numbers.

#### Clinical studies

One MAH provided 6 clinical studies evaluating metoclopramide in digestive tract explorations (capsule endoscopy and abdominal computed tomography). Gastric transit time was significantly decreased compared to the control group in 3 of the 5 studies where it was reported. In most of the studies, metoclopramide did not significantly shorten the time taken for the complete examination.

### **2.2.1.9. Paediatric population**

A procedure under Article 45 of Regulation (EC) No 1901/2006 was concluded in November 2010. This was a worksharing procedure conducted by the Member States, involving a single MAH, where data on the paediatric use was assessed. The final recommendations of the rapporteur, to be considered by each Member State, were as follows:

- The only pharmaceutical form to be used in the paediatric population (including adolescents) should be the i.v. formulation, and only for the treatment of postoperative nausea and vomiting from 1 year of age. The recommended dose should be 0.15 mg/kg body weight given as a slow injection (at least 3 minutes). The daily maximum dose should be 0.5 mg/kg body weight. If additional doses are needed, the intake should be separated by at least 6 hours.
- The other indications of the i.v. form are not recommended in the paediatric population.
- The use of metoclopramide by rectal and oral forms is not recommended in the paediatric population including adolescents.
- A contraindication in neonates should be included in all pharmaceutical forms.
- Specific warnings were to be added to the product information of all pharmaceutical forms, mainly focusing on extrapyramidal disorders.

The almost totality of the data submitted during the current procedure had already been assessed during the Article 45 procedure. The conclusions of the Article 45 procedure for each indication are summarised below, together with the new data where relevant.

#### Chemotherapy and radiotherapy induced nausea and vomiting

A total of nine studies in this indication were presented and assessed. Efficacy of metoclopramide in the treatment of CINV appears to be doubtful. There are several studies documenting inferiority to the established substances dexamethasone and 5-HT<sub>3</sub> receptor antagonists. Also, in most of the studies,

treatment regimens and doses have been used which are beyond the 0.5 mg/kg dose considered to be safe in the paediatric population.

The proposal for a second line indication was considered to be unsupported by data, and it was unclear which doses would be recommended in this scenario.

Almost all studies used the i.v. formulation, therefore it was considered unclear whether the oral formulations were at all suitable for the treatment of CINV and RINV in children.

#### Post-operative nausea and vomiting

A total of 24 studies and two Cochrane based reviews in this indication were assessed. Although the efficacy of metoclopramide has been shown in several studies, the magnitude of the effect is dependent on the timing of the dosing. Whereas many studies showed that when metoclopramide is given before surgery there is only an inconsistent, clinically marginally relevant, and almost always not statistically significant treatment effect, the studies that administered the dose after surgery were more consistent and showed a clear effect of metoclopramide.

As regards the recommended dose, the single studies and meta-analysis have shown that doses from 0.15 mg/kg body weight are efficacious. This should be recommended as the usual dose, to be repeated if needed, up to a daily dose of 0.5 mg/kg body weight in 24 hours.

It is unclear whether there is consistent efficacy in all age groups, as most positive studies have been conducted in children over 2 years of age, and smaller children have rarely, if at all, been included.

#### Other situations with nausea and vomiting

This indication refers mainly to situations of gastroenteritis. Very little data was available in this indication, and the existing data was inconsistent and was generated with different pharmaceutical forms. Therefore superiority of metoclopramide over placebo cannot be concluded.

Two additional references were submitted during the current procedure, a study and a Cochrane review. The study by Al-Ansari *et al.* (2011) compared the efficacy and safety of ondansetron for the treatment of vomiting in children with acute gastroenteritis and included 167 children between 1 and 14 years of age who were randomised to receive a single intravenous dose of either metoclopramide or ondansetron. The authors concluded that, in the sample size tested, intravenous metoclopramide did not differ from ondansetron in the treatment of persistent vomiting for children with gastroenteritis admitted for intravenous fluid hydration. The Cochrane review by Fedorowicz *et al.* (2011) looked into seven randomised controlled trials comparing antiemetics with placebo or no treatment and concluded that intravenous ondansetron and metoclopramide reduced the number of episodes of vomiting and hospital admission.

#### Gastroesophageal reflux disease

For this indication, five studies and two systematic reviews/meta-analyses were submitted. The assessment supported the conclusions of the systematic reviews that there is insufficient evidence to recommend such a treatment given that evidence of efficacy is too weak and heterogeneity among the studies is too high. It was also noted that the data submitted only included studies in infants, not in older children.

#### Other gastrointestinal motility disorders

Various studies for different indications were submitted under this sub-header. There is great heterogeneity in the studies, patient populations, therapeutic settings and outcomes. Most investigations have been performed in pharmacodynamic parameters only, and have found effects

consistent with acceleration of gastric emptying in infants and children. No effects could, however, be seen in premature infants.

However, despite the effects, it remains unclear whether a measurable clinical benefit for the patients can be concluded, as clinical parameters of therapeutic benefit have not been investigated.

#### Digestive tract explorations

Only one study was presented in support of this indication. While it showed a reduction of the time needed for endoscopic instrumentation and radiation times, it included only 18 children and therefore it does not allow for a conclusion on the efficacy of metoclopramide in this indication.

#### Migraine

This clinical setting had not been assessed during the Article 45 procedure as no paediatric data on migraine had been submitted at the time. During the current review, one relevant Cochrane review by Victor *et al.* (2003) was submitted. It concluded that only one study each for propranolol and flunarizine were identified showing efficacy as prophylactics of paediatric migraine. The remaining drugs (including metoclopramide) showed no efficacy in reduction of frequency of attacks.

### **2.2.1.10. Renal and hepatic impairment**

Elimination of metoclopramide is predominantly via urine, and approximately 20% is the unchanged drug. Metabolism is predominantly by conjugation, although some oxidative metabolites are also known. The plasma elimination half-life of metoclopramide is 5 to 6 hours, regardless of the route of administration.

#### Renal impairment

Recommendations for dose reduction for adult patients with renal impairment are included in the product information of some approved products. In most products where this is stated, a 50% reduction is recommended for all levels of impairment. Some products recommend a 50% reduction for patients with creatinine clearance (ClCr) of 10-60 ml/min and a 75% reduction for patients with creatinine clearance less than 10 ml/min.

One study (Lehmann *et al.* 1985) investigated the pharmacokinetics of a single 10 mg dose of metoclopramide in 24 patients with varying degrees of renal impairment and 8 patients with normal renal functions were included as a control group. Creatinine clearance was found to correlate with metoclopramide plasma clearance, metoclopramide renal clearance, non-renal clearance and half-life. The authors suggest a dose reduction of 50% in patients with ClCr 11-60 ml/min, and a dose reduction of 67% in patients with ClCr  $\leq$  10 ml/min, and acknowledge that this is based on single dose data which may require alterations for multiple dosing.

A similar study (Bateman *et al.* 1981) investigated the pharmacokinetics of a single 10mg dose of metoclopramide in 6 patients with chronic renal failure (in all patients with ClCr  $\leq$  15 ml/min) and found that clearance in patients with renal failure is approximately 30% of that of normal patients. This study also commented that the total change in clearance cannot be explained solely by the change in renal function, and therefore may involve changes in metabolism and/or enterohepatic circulation. The authors conclude that a dose reduction of at least 50% should be considered in patients with severe renal failure.

#### Hepatic impairment

Recommendations for a 50% reduction of dose in case of hepatic impairment are currently included in the product information of some products.

One study (Hellstern *et al.* 1987) investigated the pharmacokinetics of single oral, intravenous and rectal doses of metoclopramide (all 0.25 mg/kg) in 18 patients with histologically confirmed cirrhosis of the liver compared to 12 patients with normal liver function. The median AUC over 8 hours was similar for both groups following intravenous and rectal administration, but was significantly higher for the patients with cirrhosis following oral administration. The median oral bioavailability was also higher in patients with cirrhosis of the liver (82%) compared to patients with normal liver function (60%). The authors conclude that dose adjustments may be necessary for oral metoclopramide in patients with cirrhosis of the liver, particularly during prolonged use.

Another study (Magueur *et al.* 1991) investigated the pharmacokinetics of single oral and intravenous doses of metoclopramide in 8 patients with histologically proved alcoholic cirrhosis (Child Pugh grade C) compared with 8 patients with normal liver function. The results for both routes of administration showed a 50% lower clearance in the patients with cirrhosis, resulting in increased plasma concentrations and prolonged half-life. Volume of distribution and absolute bioavailability were similar for both groups. The authors conclude that adverse effects observed in marked hepatic impairment are likely to be due to accumulation of the drug as a result of lowered clearance and consequently a reduction in dose of 50% should be recommended in patients with severe liver cirrhosis.

Albani *et al.* (1991) studied the pharmacokinetics of metoclopramide after acute intravenous administration to 12 patients with hepatic cirrhosis (6 with and 6 without ascites) and 6 control subjects. The elimination half-life was significantly longer and total plasma clearance was significantly lower in patients with cirrhosis. The authors concluded that reduction of functional hepatic blood flow in cirrhosis patients is the probable cause of the observed alteration in metoclopramide kinetics.

### 2.2.2. Discussion

Very limited high quality data exists in support of the efficacy of metoclopramide in the majority of the indications authorised in the European Union. Much of the available data is derived from trials designed to investigate newer agents such as the 5-HT<sub>3</sub> receptor antagonists, and therefore do not always allow for a definite conclusion of the effect of metoclopramide due to the absence of a comparison to placebo. The doses, routes of administration and treatment durations of metoclopramide used in these studies are not always consistent, and only one specific dose-finding study was identified (in PONV).

#### Chemotherapy induced nausea and vomiting

The lack of placebo-controlled trial data prevents assessment of the absolute efficacy of metoclopramide in these indications. As such, based on the data assessed, the relative efficacy must be assessed in comparison to the 5-HT<sub>3</sub> receptor antagonists.

#### *Acute CINV*

Based on data from both the Jantunen meta-analysis and the randomised clinical studies assessed, metoclopramide administered intravenously or orally is consistently inferior to 5-HT<sub>3</sub> receptor antagonists for prevention of acute CINV for highly or moderately emetogenic chemotherapy.

Based on data submitted, when administered for highly emetic chemotherapy, metoclopramide appears to be effective by intravenous route at doses ranging from 6 to 10 mg/kg/day. When administered for moderately emetic chemotherapy, doses ranging from 30 to 60mg appear to be effective.

Of note, the review by Jantunen *et al.* describes the low metoclopramide doses used (20-80mg) as 'inadequate' and concludes that this may not be an appropriate comparator for 5-HT<sub>3</sub> receptor antagonists.

### *Delayed CINV*

The data presented in relation to the prevention of delayed CINV is predominantly in patients receiving moderately emetogenic chemotherapy, using oral metoclopramide at doses of 10-20 mg three or four times a day. This body of data is more consistent and indicates similar efficacy for these doses of metoclopramide given orally to the efficacy of 5-HT<sub>3</sub> receptor antagonists.

### Radiotherapy induced nausea and vomiting

Data on the use of metoclopramide in the prevention of RINV is limited. However, there are no known unique differences in the mechanism of RINV when compared to CINV, and therefore it could be appropriate to extrapolate data from CINV to RINV.

While in some cases a high dose regimen (2-10mg/kg/day) is approved for prevention of acute RINV, studies have been conducted using 10 mg three times a day and the efficacy of this posology is not questioned.

### Post-operative nausea and vomiting

The data presented in support of the effect of metoclopramide in post-operative nausea and vomiting indicates that it has similar efficacy to other active substances authorised in this indication. The almost totality of the data relates to the intravenous administration of metoclopramide, and in the majority of the studies assessed, a 10 mg dose was used.

### Nausea and vomiting associated with migraine

The data presented is indicative of the efficacy of metoclopramide in acute migraine induced nausea and vomiting based on its anti-emetic properties. In addition, due to its prokinetic properties, metoclopramide may also play a role when given orally in combination with analgesics. Data on the dosing seems to indicate that individual doses of metoclopramide higher than 10mg do not result in increased efficacy.

### Nausea and vomiting of other origins

The data presented is limited and was generated in different settings during which nausea and vomiting may occur. While it is difficult to conclude on absolute efficacy of metoclopramide in these individual settings, when taken together, the data are indicative of an effect on nausea and vomiting of different aetiologies.

### Gastrointestinal motility disorders

The review by Lee *et al.* provides a complete overview of the evidence of efficacy in diabetic gastroparesis. While metoclopramide was found to improve gastric emptying and relieve symptoms in diabetic and idiopathic gastroparesis in short term treatment when compared to placebo, no consistent benefit was observed in the long term. Gastroparesis is often a chronic disorder, for which long term treatment is necessary, therefore existing data cannot be considered supportive of the use in this indication.

### Gastroesophageal reflux disease and dyspepsia

Based on the data presented, there is little evidence of efficacy of metoclopramide in treatment of gastroesophageal reflux disease or dyspepsia and existing data is not consistent in terms of effect.

Furthermore, existing studies included a very small number of patients and focused on a small duration of treatment. It is also noted that there are other well-established agents available for this indication, including proton pump inhibitors and H<sub>2</sub> receptor antagonists, for which a positive benefit-risk balance has been clearly demonstrated for acute and chronic use. Both gastroesophageal reflux disease and

dyspepsia may be chronic diseases, and therefore existing data cannot be considered sufficient to support the use in these indications.

#### Adjuvant to surgical and radiological procedures

Very limited data exists in support of the efficacy of metoclopramide in this indication, and the existing data is not consistent. The studies assessed seem to indicate that metoclopramide reduces gastric transit time, but this did not affect the time taken to complete the examination. On the basis of such limited and inconsistent data, it is not possible to conclude positively on the efficacy of metoclopramide in this indication.

#### Paediatric population

The majority of the efficacy data submitted during the current procedure had already been assessed during the previous paediatric worksharing procedure under Article 45 of Regulation (EC) No 1901/2006, and the new data did not add relevant new elements to the previous assessment.

There is sufficient evidence of efficacy of metoclopramide in the treatment of post-operative nausea and vomiting in the paediatric population. For this indication, only the intravenous formulation is of relevance, in line with the outcome of the procedure under Article 45 of Regulation (EC) No 1901/2006.

With regards to the delayed CINV, the Committee agreed with the previous assessment that the data is limited and shows that metoclopramide is inferior to 5-HT<sub>3</sub> receptor antagonists. However, it also took into consideration the recommendations of the British National Formulary for children (BNFc), which has been validated against emerging evidence, best practice guidelines and advice from a network of clinical experts. According to the BNFc, in patients at low risk of emesis, pre-treatment with metoclopramide continued for up to 24 hours after chemotherapy is often effective. For this indication, prophylaxis is usually initiated with a 5-HT<sub>3</sub> receptor antagonist before chemotherapy and is followed by metoclopramide (usually oral) prescribed for a further 24-48 hours. This therapeutic alternative may be of particular relevance due to the association between prolonged use of 5-HT<sub>3</sub> receptor antagonists and adverse effects of constipation and headache, which may be severe and poorly tolerated. Given the limited therapeutic alternatives for the paediatric population in this setting, it may be acceptable that delayed CINV is retained as a second line option despite the lack of robust efficacy data. For this particular indication in the paediatric population, both the parenteral and the oral pharmaceutical forms may be appropriate.

#### Renal and hepatic impairment

Established renal failure is defined as  $\text{ClCr} \leq 15$  ml/min, therefore this cut-off should be included in any dosing recommendations. In this population, and based on the studies submitted, the clearance of metoclopramide has shown to be significantly impaired. As such, a dose reduction of 75% would be necessary. However, for patients with moderate to severe impairment ( $\text{ClCr}$  15-60 ml/min), a 50% reduction remains appropriate.

The available evidence from small single dose studies suggests that metoclopramide clearance is substantially reduced in patients with hepatic cirrhosis. There appears to be no pharmacokinetic data on multiple-dosing, nor is there comparative data for different levels of hepatic impairment. In the absence of such data, no specific recommendation can be issued for lower levels of hepatic impairment. For severe hepatic impairment, the existing recommendation for 50% dose reduction is appropriate.

## **2.3. Clinical safety**

Several MAHs submitted analyses of the safety data on their products, including spontaneous reports, data from clinical trials and epidemiological studies. The largest dataset of spontaneous reports was submitted by the originator, and is briefly described below. The assessment of the remaining submissions was not found to differ significantly from the below.

### **2.3.1. Results**

#### *Summary of spontaneous cases*

In the period up to 10 December 2011, a total of 4005 spontaneous cases were recorded in the MAH international database, corresponding to 9282 adverse drug reactions (ADR). Of these, 72% (2877) were medically confirmed.

- Extrapyrimal disorders (2442 ADRs corresponding to 1749 cases, 44% of the total number of cases).
- Decrease of consciousness (332 ADRs)
- Allergic reactions (202 ADRs)
- Nausea and vomiting (176 ADRs), mostly related with lack of efficacy.
- Anaphylactic reactions (171 ADRs)
- Tremors (152 ADRs)
- Respiratory disorders (126 ADRs)
- Generalised convulsive disorders (122 ADRs)

Overall, in comparison to adults, reporting rate was calculated to be 4 times higher in children and 2 times lower in the elderly. Methaemoglobinaemia was almost exclusively reported in children, although the number of cases is low.

#### **2.3.1.1. Neurological adverse events**

The most frequently reported serious neurological ADRs were: extrapyramidal disorders, dyskinesia, dystonia, convulsion, hypertonia, tremor. The rate of administration of the parenteral formulations appears to be a risk factor for a range of adverse events such as akathisia.

Serious neurological effects were reported with all routes of administration, but more frequently with the oral formulations. In most cases reactions occurred shortly (1 to 2 days) after the administration of metoclopramide. These effects appear to occur more readily when patients are taking repeated doses in comparison to single dose administration.

Compared to adults, it is noted that reporting rates were higher in children for extrapyramidal disorders (6 times higher), decrease of consciousness (5 times higher) and for generalised convulsive disorders (4 times higher).

The elderly appear to be at increased risk for development of tardive dyskinesia, which in some cases was irreversible. In contrast, non-tardive effects tend to be reversible upon discontinuation of metoclopramide or appropriate treatment.

#### *Epidemiological data*

Epidemiological studies have been conducted in different countries to evaluate the risk of tardive dyskinesia associated with metoclopramide use in adults. Only retrospective studies were conducted based on chart reviews of patients referred for tardive dyskinesia and on prescriptions databases and have been summarized in a review (Rao *et al.* 2010).

In a recent retrospective chart review performed on 434 patients (77% women, 64 + 15 years old) evaluated for tardive dyskinesia in a Parkinson's Disease and Movement Disorders Clinic in the US, metoclopramide accounted for 39.4% of tardive dyskinesia (Kenney *et al.* 2008).

In a study conducted from a Veterans administration centre using an exposed/unexposed design, the prevalence of tardive dyskinesia was found to be 29% in 51 metoclopramide users and 17.6% in 51 matched non-users. The relative risk for tardive dyskinesia was 1.67 (95% CI, 0.93 to 2.97), and the relative risk for drug induced parkinsonism was 4.0 (95% CI, 1.5 to 10.5) (Ganzini *et al.* 1993).

In addition, the studies conducted from prescription databases have calculated reporting rate from spontaneous reports of extrapyramidal symptoms using total number of prescription as denominator. In the UK from 1967 to 1982, the reporting rate of extrapyramidal symptoms was 1 in around 33,000 prescriptions and was mostly observed in 10-29 years (Bateman *et al.*, 1985)). In Sweden from 1977 to 1981, the reporting rate of tardive dyskinesia was 1 in 17,800 prescriptions and cases were observed in patients 69 years old or over (Wiholm *et al.* 1984).

A retrospective study of 79 case reports of tardive dyskinesia recorded in the FDA adverse event reporting system showed that cases represented older (60 + 21 years old) women (62%) with a long duration of use of metoclopramide (813 + 961 days). Among these cases, coprescriptions of neuropsychiatric drugs were found in 37% of the cases and 22% had a preexisting disease such as diabetes (Shaffer *et al.* 2002).

### 2.3.1.2. Cardiovascular adverse events

The most frequently reported serious cardiovascular reactions included: shock, hypotension, cardiac arrest, tachycardia, bradycardia, hypertension, cardio-respiratory arrest, circulatory collapse.

Serious cardiovascular effects occurred with all metoclopramide formulations, however the majority of reports corresponded to intravenous use and events occurred shortly after administration. Distribution of cases by age group shows a predominance of reports in the adult population.

The rate of administration of the parenteral formulations appears to be a risk factor for a range of adverse events such as hypotension.

A few cases of QT prolongation have been reported although causality is difficult to assess as cases were heavily confounded. Considering how extensively metoclopramide is used, the number of cases is too small to indicate an association between metoclopramide and QT prolongation.

### 2.3.1.3. Overdose

A high number of cases of overdose have been reported. The majority of reports occurred in France and involved use of the concentrated oral drop formulation in the paediatric population.

Table 1 Distribution of spontaneous cases of overdose in the originator's database (up to 10 December 2011) per population.

<b>No. cases</b>	<b>Children</b>	<b>Adult</b>	<b>Elderly</b>	<b>Unknown</b>	<b>Total</b>
Total of cases	474	94	7	23	<b>598</b>

Cases involving extrapyramidal disorders have been reported in a context of overdose as well as with no overdose.

Table 2 Distribution of cases of extrapyramidal disorders in the originator's database (up to 10 December 2011)

<b>Cases by population and overdose/non overdose</b>	<b>Overdose</b>	<b>Non overdose</b>	<b>Total</b>
[0 - 18 years[	339	494	<b>833</b>
[18 - 65 years[	57	626	<b>683</b>
[> 65 years]	2	134	<b>136</b>
Unknown	7	90	<b>97</b>
<b>Total</b>	<b>405</b>	<b>1344</b>	<b>1749</b>

In the paediatric population, the oral liquid formulations (mainly with concentration higher than 1 mg/ml) are associated with an increased risk of overdose and ADRs.

### 2.3.1.4. Paediatric population

The previous assessment under Article 45 had already concluded the following regarding safety in the paediatric population:

- In pre-term and term neonates, clearance of metoclopramide is diminished and half-life and plasma concentrations are increased.
- The overall evaluation of safety showed that there is a considerable burden of adverse reactions attributed to central nervous system related effects of metoclopramide, especially to the occurrence of extrapyramidal reactions. This risk is not only related to overdosing and poisoning, but, to a considerable part, also occurs when the currently recommended dosing instructions (maximum single dose of 0.15 mg/kg, maximum daily dose of 0.5 mg/kg, additional doses after 6 hours at the earliest) are adhered to.
- Extrapyramidal disorders usually occur at an early time point of treatment.
- There is no clear indication whether there is a differential risk in the different age groups, however, the number of reported events (especially for central nervous system related events) is clearly highest in the youngest age group. A literature review and the poor methodology in most pharmacoepidemiological studies were also not able to differentiate properly between age groups.
- Due to immaturity of drug metabolism and blood-brain barrier in very young children, metoclopramide should not be used in children below the age of 1 year and should be contraindicated for neonates.
- The only pharmaceutical form to be used in children should be the intravenous form for the treatment of postoperative nausea and vomiting (PONV) for children over 1 year of age. The use of the other formulations and the use for other indications in the paediatric population are not recommended. This recommendation was based on the fact that the studies supporting the PONV indication were conducted using the injectable solution and this is the most appropriate route of administration for this indication.

It was however noted during the current assessment under Article 31 that, should other indications be considered to have a positive benefit-risk balance in the paediatric population (see section 2.2.2), the use of other routes of administration may be clinically appropriate.

In the paediatric population, oral liquid formulations (mainly with concentration higher than 1 mg/ml) were associated with an increased risk of overdose and ADRs (see section 2.3.1.3). Dose accuracy is particularly important in children, and may be harder to achieve with high concentration oral solutions and/or less precise measuring devices. Therefore, in order for oral liquid formulations to be used safely in children, appropriate risk minimisation measures need to be put in place to address the risk of

overdose. These should include restrictions on the concentration of the product and provision of an appropriate measuring device.

### 2.3.1.5. Pregnancy and lactation

#### *Pregnancy*

Matok *et al.* (2009) investigated the safety of metoclopramide use during the first trimester of pregnancy by linking computerized database of medications dispensed from 1998 to 2007 with computerized databases containing maternal and infant hospital records in the southern district of Israel. A total of 81,703 infants were included, 4.2% of which were exposed to metoclopramide. Exposure to metoclopramide in the first trimester was not associated with significantly increased risks of major congenital malformations (OR = 1.04; 95% CI 0.89 - 1.21), low birth weight (OR = 1.01; 95% CI, 0.89 - 1.14), preterm delivery (OR = 1.15; 95% CI, 0.99 to 1.34), or perinatal death (OR = 0.87; 95% CI 0.55 - 1.38).

Berkovitch *et al.* (2002), in a prospective study conducted in women calling teratogen information centers about metoclopramide exposure in Israel, Italy, Brazil, and Canada, enrolled 175 women exposed to metoclopramide and paired to women exposed to non-teratogens. Metoclopramide use during the first trimester of pregnancy was not associated with an increased risk of major malformations (RR=0.91 95% CI [0.34-2.45]), spontaneous abortions (RR=0.80 95% CI [0.22-2.93]), or decreased birth weight (p=0.22), but was associated with a higher rate of premature birth (RR=3.37 95% CI [1.12-10.12]).

Sørensen *et al.* (2000) investigated in Denmark the safety of metoclopramide during pregnancy by linking the prescription database of North Jutland in Denmark to the Danish medical birth registry and the Danish hospital discharge registry from 1991 to 1996. 309 women who had taken at least a prescription of metoclopramide were identified and 13,327 women who had no prescription of reimbursed drugs during pregnancy were used as reference. Metoclopramide use during pregnancy was not associated with an increased risk of malformations (OR=1.11; 95% CI 0.6 - 2.1); low birth weight (OR=1.79; 95% CI: 0.8 - 3.9) or preterm delivery (OR=1.02; 95 CI: 0.6 - 1.7).

#### *Lactation*

Based on a maternal metoclopramide exposure of 30 mg, it has been estimated that the infant would receive a maximum of 5% of the maternal weight-adjusted dosage (Kauppila *et al.* 1983). Thus metoclopramide is excreted in breast milk at low level.

Adverse events reported in breastfed infants exposed through breast milk include gastrointestinal disorders, somnolence, agitation/restlessness/nervousness/impatience, convulsion/involuntary movements/hypertonia and allergic type reactions. All were reported in the context of off label use (increase of lactation). Some of the cases have a chronology suggestive of a causal relationship.

In the literature, about 200 newborns exposed to metoclopramide via breast milk have been reported in efficacy controlled trials (Zuppa *et al.* 2010). Among these 200 newborns, side effects were studied in about 70 newborns and only 2 events were reported (mild and transient intestinal discomfort).

### 2.3.1.6. Drug interactions associated with the CYP 2D6 isoenzyme

As previously indicated, elimination of metoclopramide is predominantly renal and approximately 20% as the unchanged drug. Metabolism is predominantly by conjugation, although some oxidative metabolites are also known. As such, metabolism by CYP450 enzymes is not likely to be the main route of elimination of metoclopramide. Studies have shown that metoclopramide is a substrate and an inhibitor of CYP2D6, although this has not been specifically confirmed *in vivo*.

One study (Vlase *et al.* 2006) investigated the pharmacokinetic interaction between fluoxetine (a potent inhibitor of CYP2D6) and metoclopramide in healthy volunteers. In this study, pre-treatment with a single daily dose of 60mg fluoxetine for 8 days prior to the administration of 20mg metoclopramide significantly increased their exposure (C<sub>max</sub> (1.4 fold) and AUC (1.9 fold)) to metoclopramide. The pre-treatment regime was chosen as this has been shown to achieve similar plasma concentrations to long term administration of 20mg fluoxetine.

In the post-marketing setting, cases of drug interaction with a co-suspect drug known to be an inhibitor of CYP2D6 (e.g. citalopram, escitalopram, fluoxetine, paroxetine, duloxetine, terbinafine) have been reported.

Van der Padt *et al.* (2006) described two cases of acute dystonic reactions to metoclopramide in patients who were homozygous carriers of CYP2D6 variant alleles, making them poor metabolisers with respect to this isoenzyme. Both cases reported successful treatment of the dystonic reaction, and no further reactions after stopping metoclopramide.

### 2.3.2. Discussion

Metoclopramide has long been associated with a risk of serious neurological adverse reactions such as acute extrapyramidal symptoms and irreversible tardive dyskinesia. From the data assessed, it appears that the risk of acute dystonias is increased when using high doses, and is higher in children than in adults. The elderly appear to be at particular risk of developing tardive dyskinesia following long-term treatment which in some cases may be irreversible. The slow administration of intravenous doses as a slow bolus over at least 3 minutes lowers the risk of all dystonic reactions.

In children there is also a significant number of reported cases of overdose. It is noted that the majority of cases involves the use of high concentration oral liquid formulations, which are currently approved under a number of different formulations (oral drops, oral solution, syrup) with very different concentrations and a range of administration devices. This raises an issue of dose accuracy and reproducibility, particularly with high concentration formulations, and may explain at least partially the reason behind the reports of accidental overdose in the paediatric population. It is possible that there is unintended misuse of the high concentration oral liquid formulations, leading to the inadvertent administration of doses higher than intended. If however risk minimisation measures are put in place to allow accurate dosing and address the risk of overdose, oral liquid formulations remain an important and suitable alternative for the paediatric population.

Although serious cardiovascular reactions have been reported with metoclopramide (mainly associated to the intravenous administration), no new significant signals have been identified. The Committee considered the proposal by one MAH to explicitly restrict intravenous administration to locations where resuscitation equipment is available, but noted that most places where intravenous drugs are administered will already have such equipment.

The published epidemiological studies conducted in different countries on the safety of metoclopramide use during pregnancy consistently showed the absence of association between exposure during pregnancy and risk of major congenital malformations. Metoclopramide can therefore be used during pregnancy, if clinically justified. However, a few cases of extrapyramidal reactions in newborns exposed to metoclopramide before delivery have been identified. Therefore the risk to newborns cannot be excluded and metoclopramide should be avoided at the end of pregnancy.

Metoclopramide is excreted in breast milk, and although the available data does not raise concerns, effects in the breast fed infant cannot be excluded. Therefore it would be appropriate to not to use metoclopramide during breastfeeding.

The available evidence in relation to CYP2D6 polymorphisms, when taken together with the data on interactions with CYP2D6 inhibitors, is suggestive that whilst CYP2D6 metabolism is not the main metabolic pathway for metoclopramide, the inhibition of this pathway due to polymorphisms or pharmacokinetic interactions with other drugs may potentially be clinically significant. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

## **2.4. Risk management plan**

The CHMP did not require the MAH to submit a risk management plan.

The CHMP, having considered the data submitted, is of the opinion that in addition to product information amendments which include the use of the minimum effective dose and the limitation of treatment duration, the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- Limiting the maximum concentration/dosing in certain formulations to ensure that patients are not unintentionally exposed to doses higher than the single recommended dose for the product.
- Oral liquid formulations intended to be used in children must be supplied with an appropriate measuring device (e.g. graduated oral syringe) to ensure accurate measuring of the dose and avoid accidental overdosing.

## **2.5. Overall benefit/risk assessment**

Limited data exists on the efficacy of metoclopramide in the different therapeutic indications authorised in the European Union; however, when taken together, it is indicative of the efficacy of the product in the management of nausea and vomiting of different origins. For the majority of the indications, there is clinical data evaluating the efficacy of the posology of 10 mg three times a day. While in some cases higher doses may be currently authorised, with the exception of acute CINV the existing data does not clearly indicate that higher individual doses result in increased efficacy. In addition, data is indicative that the burden of adverse reactions is increased with dose. Therefore, in order to minimise the risk of serious neurological adverse reactions such as acute extrapyramidal symptoms and irreversible tardive dyskinesia, the dose should be restricted to the minimum effective dose, which for adults is considered to be 10 mg three times daily.

### *Adults*

For therapeutic indications such as *delayed CINV*, *prevention of RINV*, *prevention of PONV* and *symptomatic treatment of nausea and vomiting including migraine induced nausea and vomiting*, data is indicative of efficacy at low doses (10mg, three times daily) which minimise the risk of serious neurological adverse reactions. Therefore, for these indications the Committee considered benefit-risk balance to be positive.

For the indication *acute CINV*, while there is some data indicative of efficacy, it requires the intravenous use of high doses of metoclopramide which carry higher risks not only of neurological but also cardiovascular adverse reactions (including cardiac arrest). For this reason, the Committee considered that the benefit-risk balance of metoclopramide in this indication is negative and recommended that it is deleted.

Considering the newly recommended posology, parenteral formulations with concentration higher than 5mg/ml currently approved in the European Union (mainly for the management of acute CINV) will not be suitable for administration of the 10mg dose, are therefore considered to have a negative benefit-risk balance and should be revoked.

For the indications *gastrointestinal motility disorders including gastroparesis and gastroesophageal reflux disease and dyspepsia*, the Committee noted that these are essentially chronic conditions for which long term use is often required. There is no data submitted to support the efficacy of metoclopramide in the required treatment duration, but there is evidence that the above mentioned risks are increased with prolonged treatment. Therefore the Committee considered that the benefit-risk balance of metoclopramide in these indications is negative.

For the indication *adjuvant to surgical and radiological procedures*, very limited efficacy data exists, and the existing data is not consistent. The studies assessed seem to indicate that metoclopramide reduces gastric transit time, but this did not translate into a clinically meaningful outcome (time taken to complete the examination). In the absence of an established benefit, and taking into account the safety profile of metoclopramide, the Committee considered that the benefit-risk balance of metoclopramide in this indication is negative.

### *Children*

Very limited information exists to support the efficacy of metoclopramide in the paediatric population, in the majority of the indications. The exception is the *treatment of established post-operative nausea and vomiting*, which had already been recommended to be maintained in a previous worksharing procedure under Article 45 of Regulation (EC) No 1901/2006.

While endorsing the conclusions of the previous assessment, the CHMP also took note of the fact that, in particular for the treatment of delayed CINV which can be quite a debilitating condition, there are limited alternatives available for the paediatric population. Metoclopramide has long been included in the British National Formulary for children (BNFc), which has been validated against emerging evidence, best practice guidelines and advice from a network of clinical experts. Therefore the Committee considered that, based on long term experience of use and the clinical need for treatment options in the paediatric population, the benefit-risk balance of metoclopramide for the *prevention of delayed CINV* in the paediatric population can be considered positive. For this indication and population, it is considered particularly important that oral formulations are available.

However the safety data seems to indicate that methaemoglobinaemia occurs almost exclusively in children, and that children are also at higher risk of serious neurological adverse reactions. Therefore use of metoclopramide should be reserved for situations where alternative treatments have not been effective or cannot be administered. Thus, for both *treatment of established post-operative nausea and vomiting* and *prevention of delayed CINV* in children, the use of metoclopramide should be reserved as a second line option.

### *Oral liquid formulations*

The majority of cases of accidental overdose occurred in children and involve the use of high concentration oral liquid formulations. This may be due to an issue of dose accuracy and reproducibility, unclear information on dosing and possibly difficulties measuring and administering the correct dose, particularly with high concentration formulations and poorly validated devices. Therefore the Committee considered that it is an important risk minimisation measure to restrict the maximum concentration of oral liquid formulations to 1 mg/ml, to ensure that clear instructions are given in the product information on posology for paediatric patients and that these oral liquid formulations are supplied with an appropriate measuring device such as a graduated oral syringe.

### *Suppositories*

It was noted by the Committee that a formulation of suppositories dosed at 20mg is currently approved in some Member States. As previously described, there is no evidence that doses above 10mg result in higher efficacy. However, the risk of serious neurological adverse reactions is increased.

Considering the recommendation for posology to be defined as 10mg three times a day and the fact that this pharmaceutical form does not allow for adjustment of dose, the Committee considered that the benefit-risk balance of the suppositories dosed at 20mg is negative.

## **2.6. Re-examination procedure**

Following the adoption of the CHMP opinion in July 2013, a request for re-examination was received from one MAH concerned by the procedure.

### **Detailed grounds for re-examination submitted by the MAH**

The grounds for re-examination submitted by the MAH were as follows:

- Disagreement with the CHMP recommendation for revocation of oral liquid formulations with concentration higher than 1 mg/ml.

The MAH in question considered that oral liquid formulations with concentration higher than 1 mg/ml continue to be useful for adult patients. In particular, the MAH pointed out that, using a formulation containing 4 mg/ml, the individual dose for adults requires 15 to 30 drops and allows adjustment for adults with different body weights or with renal or hepatic impairment. It was also highlighted that for an oral liquid formulation with concentration 1 mg/ml, 60 to 120 drops per dose would need to be used and this is not practicable for adult patients.

The MAH further argued that in case of nausea drops are easier to swallow than tablets.

Furthermore, it was stated that the onset of action is faster with the solution in comparison to that of tablets, as tablets have first to be dissolved in the gastrointestinal tract.

While considering that the concentration 4 mg/ml is appropriate for adults, the MAH recognised that it is too high for children and therefore proposed the following measures to avoid the risk of overdose in children:

- To add a contraindication in children under 18 years of age
- To add the statement 'for adults' on the labelling of oral liquid formulations with concentration higher than 1 mg/ml.

No data was submitted by the MAH in support of the above claims.

### **CHMP conclusion on grounds for re-examination**

In its July 2013 opinion, the CHMP concluded that oral liquid formulations of metoclopramide up to 1 mg/ml were suitable for use in the adult population in the following indications:

- Prevention of delayed chemotherapy induced nausea and vomiting (CINV)
- Prevention of radiotherapy induced nausea and vomiting (RINV).
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting. Metoclopramide can be used in combination with oral analgesics to improve the absorption of analgesics in acute migraine.

For all of these indications, the recommended single dose for adults is 10 mg, up to three times daily. This posology applies to all oral formulations and is not dependent on body weight.

In respect of dose adjustment for renal and hepatic impairment, while it is correct that oral liquid formulations offer advantage over solid pharmaceutical forms (e.g. tablets), higher concentrations (such as 4 mg/ml) do not have additional advantage over the proposed 1 mg/ml. Both the 50% and the 75% dose reductions recommended, respectively, in hepatic and renal impairment are easily

achievable with the 1 mg/ml liquid formulations (5 ml and 2.5 ml, respectively).

In its July 2013 opinion, the CHMP also recommended that oral liquid formulations be supplied with an appropriate measuring device such as a graduated oral syringe. If an appropriate measuring device is used as recommended, there will be no need to count drops. Using a device such as a graduated oral syringe may even be more convenient than counting drops and it ensures accurate and reproducible dosing in any situation, including when doses are reduced due to renal or hepatic impairment.

In its grounds for re-examination, the MAH also argued that in case of nausea drops are easier to swallow than tablets. There is no clinical data available to allow for a discussion on this point. It is acknowledged that some patients may prefer an oral liquid formulation to a solid pharmaceutical form due to personal preferences, palatability, etc., and the oral liquid formulations with concentration 1mg/ml are suitable for this purpose.

Limited data exists on the onset of action of oral liquid formulations in comparison with tablets. An oral bioequivalence study of metoclopramide tablets compared to liquid (Wright GJ, 1982) showed that  $C_{max}$  and  $T_{max}$  are not significantly different for the two oral formulations. Therefore, the Committee considered that the available evidence does not support the assumption that oral liquid formulations have a faster onset of action than tablets.

The MAH considered in its grounds that for oral liquid solutions a concentration of 4 mg/ml is too high for children and that there is a risk of overdose in this population. In order to minimise the risk of overdose in children, the MAH proposed to add the statement 'for adults' in the label of oral liquid formulations with concentration > 1 mg/ml, and a contraindication in the paediatric population. The Committee noted this proposal from the MAH, but it also took note of the fact that, even if not specifically approved for paediatric use, high concentration oral liquid formulations are associated with risks in this population. Post marketing data is suggestive of unintended misuse of these formulations (oral drops, oral solution, syrup), approved under a range of concentrations and with a range of administration devices potentially leading to the inadvertent administration of doses higher than intended. In this scenario where the unintended misuse is already taking place, to include a contraindication in the product information alongside a statement in the labelling is unlikely to be sufficient to change administration habits.

In conclusion, the Committee considered that oral liquid formulations with concentration 1 mg/ml are suitable for all situations mentioned, and that the availability of higher concentrations carries a risk of overdose in the paediatric population that is unlikely to be resolved by the proposed changes to the product information.

Divergent positions are appended to this report.

## **2.7. Communication plan**

As part of this referral procedure, the CHMP agreed on the wording of a 'Dear Healthcare Professional' communication designed to inform prescribers of the amendments recommended to the product information, and of the revocation of certain formulations, to be sent to relevant health care professionals within 1 month of the publication of the Commission Decision.

## **2.8. Changes to the product information**

The Committee recommended the following changes to the summary of product characteristics:

- Section 4.1 – deletion of indications with a negative benefit-risk balance and rewording of the remaining indications in accordance with the above.

- Section 4.2 – amendment of the posology information to reflect new dosing recommendation for children and adults, including a dosing table for children, maximum treatment duration and dose adjustment for patients with renal and hepatic impairment.
- Section 4.3 – contraindications
- Section 4.4 – inclusion of new warnings on neurological disorders, methaemoglobinaemia and cardiac disorders.
- Section 4.5 – revised information on interaction with other medicinal products
- Section 4.6 – revised information on pregnancy and breastfeeding.
- Section 4.7 – Inclusion of information on possible adverse events that could interfere with ability to drive and use machines
- Section 4.8 – Updating of the list of known adverse reactions
- Section 4.9 – Inclusion of information on symptoms and management of overdose
- Section 5.2 – Inclusion of pharmacokinetic information on renal and hepatic impairment

### 3. Overall conclusion

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for metoclopramide-containing medicinal products.
- The Committee considered the totality of the data submitted in support of the efficacy and safety of metoclopramide.
- The Committee considered that metoclopramide is associated with a risk of serious adverse events, including neurological adverse events such as extrapyramidal symptoms and irreversible tardive dyskinesia. The risks are increased when using high doses or during long-term treatment, and in particular for extrapyramidal symptoms the risk is higher in children than in adults.
- The Committee considered that the risk of serious neurological adverse events can be minimised by using lower doses of metoclopramide and limiting treatment duration. The Committee also considered that the risk of unintentional overdose and associated adverse events in children can be lowered by limiting the maximum concentration of oral liquid formulations.
- The Committee noted that the available data do not support clinically significant efficacy for the indications which require long term use ('gastrointestinal motility disorders including gastroparesis', 'gastroesophageal reflux disease and dyspepsia') and for the indication 'adjuvant to surgical and radiological procedures'.
- The Committee also noted that the data supporting the therapeutic indication 'prevention of acute chemotherapy induced nausea and vomiting' is indicative of efficacy but requires the use of high doses.
- In view of the available data the Committee concluded, subject to the amendments to the product information and implementation of the risk minimisation measures, that the benefit-risk balance of metoclopramide-containing products:
  - Is favourable in adults for 'prevention of delayed chemotherapy induced nausea and vomiting' (oral and rectal routes)
  - Is favourable in adults for 'prevention of radiotherapy induced nausea and vomiting' (parenteral, oral and rectal routes)

- Is favourable in adults for 'prevention of post-operative nausea and vomiting' (parenteral route only)
- Is favourable in adults for 'symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting' (parenteral route) and 'symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting. Metoclopramide can be used in combination with oral analgesics to improve the absorption of analgesics in acute migraine' ((oral route)
- Is favourable in children between 1 and 18 years of age for 'prevention of delayed chemotherapy induced nausea and vomiting, as second line option' (parenteral and oral routes)
- Is favourable in children between 1 and 18 years of age for 'treatment of established post-operative nausea and vomiting, as second line option' (parenteral route only)
- In view of the available data the Committee also concluded that the benefit-risk balance of metoclopramide-containing products:
  - Is not favourable in children under 1 year of age for any indication.
  - Is not favourable for 'prevention of acute chemotherapy induced nausea and vomiting'
  - Is not favourable for 'gastrointestinal motility disorders, including gastroparesis'
  - Is not favourable for 'gastroesophageal reflux disease and dyspepsia'
  - Is not favourable for oral liquid formulations with concentration higher than 1mg/ml
  - Is not favourable for parenteral formulations with concentration higher than 5mg/ml
  - Is not favourable for rectal formulations dosed at 20mg

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

- The revocation of the marketing authorisations for:
  - oral liquid formulations with concentration higher than 1mg/ml
  - parenteral formulations with concentration higher than 5mg/ml
  - rectal formulations dosed at 20mg
- The variation to the terms of the marketing authorisation for the remaining metoclopramide-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 CHMP opinion. Oral liquid formulations shall be supplied with an appropriate measuring device such as a graduated oral syringe.

The Committee, as a consequence, concluded that the benefit-risk balance of metoclopramide-containing medicinal products remains positive, taking into account the changes to the product information and risk minimisation measures recommended.

## 4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.

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**Appendix I**

*Divergent positions*

## ***Referral under Article 31 of Directive 2001/83/EC – re-examination***

Procedure No: EMEA/H/A-31/1321

Metoclopramide-containing medicinal products

### **Divergent statement**

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the revocation of the Marketing Authorisation for Metoclopramide oral liquid formulations with concentration higher than 1mg/ml. The reasons for divergent opinion were as follows:

Metoclopramide 4mg/ml oral liquid formulation is useful in adults to achieve the recommended single dose of 10mg. While the recommended dose can also be administered with the 1mg/ml oral liquid formulations, this requires availability of a suitable measuring device and may also lead to dosing errors, under-dosing and compliance issues.

Metoclopramide oral formulations in concentration higher than 1mg/ml can lead to accidental overdosing mainly in children. Most overdose case reports occurred in one member state, where only drop formulations with concentrations lower than 4mg/ml were available. Furthermore, from the review of the safety data it appears that the number of overdose cases in the population below 18 years of age was not significantly higher in patients treated with metoclopramide oral drops or oral solution than in patients treated with tablets.

After finalisation of the referral under Article 31 of Directive 2001/83/EC recommending restrictions of the therapeutic indications for metoclopramide, use of metoclopramide will be restricted to very specific therapeutic areas, which is expected to prevent widespread and uncritical use of metoclopramide.

In children aged 1-18 years only one indication (i.e. treatment of delayed CINV) remains for oral metoclopramide products, and only as a second line option. There is a suitable oral liquid formulation for children (1mg/ml) and all higher strengths are to be contraindicated in children. As far as the use of oral liquid metoclopramide in children is concerned, this seems a very clear message that can be effectively communicated to health care professionals via a DHPC agreed as a part of Article 31 Referral procedure.

Contraindicating the use of metoclopramide 4 mg/ml oral liquid formulations in children up to 18 years of age is regarded as an appropriate risk minimization measure. The potential risk of medication error, off-label use in children and overdose in children needs to be adequately reflected in a Risk Management Plan for metoclopramide oral liquid formulations with a concentration higher than 1mg/ml.

In addition, adult and paediatric formulations in different strengths, as suitable for the respective patients group, are available for many medicines in the EU. Given that with all these medicines there is a potential risk of inadvertent administration of doses higher than intended, it could be argued that restricting the concentration to 1mg/ml also for use in adults does not seem an adequate risk minimisation measure.

In summary, it is considered that the benefit risk balance of metoclopramide oral liquid formulations 4mg/ml is positive if contraindicated in children up to 18 years of age and thus the marketing authorisation for oral liquid formulations 4mg/ml should be maintained.

**CHMP members expressing a divergent opinion:**

Radka Montoniová	23 October 2013	Signature: .....
Romaldas Mačiulaitis	23 October 2013	Signature: .....
Pieter de Graeff	23 October 2013	Signature: .....
Hubert Leufkens	23 October 2013	Signature: .....
John Joseph Borg	23 October 2013	Signature: .....
Andrea Laslop	23 October 2013	Signature: .....

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In summary, it is considered that the benefit risk balance of metoclopramide oral liquid formulations 4mg/ml is positive if contraindicated in children up to 18 years of age and thus the marketing authorisation for oral liquid formulations 4mg/ml should be maintained.

Karsten Bruins Slot	23 October 2013	Signature: .....
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