Annex II

Scientific conclusions and grounds for revocation / variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of metoclopramide-only containing medicinal products (see Annex I)

Background information

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-HT3) 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 the concerned 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 reported with the formulations for intravenous use.

A paediatric worksharing procedure under Article 45 of Regulation (EC) No 1901/2006[1] to assess information from paediatric studies with metoclopramide has been concluded in 2010 with a recommendation that Member States should introduce the following changes to the product information:

- Contraindication in neonates;

[1] *Rapporteur's public paediatric assessment report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No. 1901/2006, as amended, 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

- 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.

Efficacy data

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_3 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_3 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_3 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_3 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_3 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 H2 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_3 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_3 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_3 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 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 (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.

Safety data

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 administrated 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 no raise concerns, effects in the breast fed infant cannot be excluded. Therefore it would be appropriate 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.

Risk Minimisation Measures

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.

Overall conclusion

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 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 the 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 alternative treatments 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.

The CHMP endorsed a communication i.e. Dear Healthcare Professional Communication (DHPC), to rapidly communicate the outcome of the present review.

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

Re-examination procedure

The MAH disagreed with the CHMP recommendation for revocation of oral liquid formulations with concentration higher than 1 mg/ml. The MAH considered that oral liquid formulations with concentration higher than 1 mg/ml continue to be useful for adult patients, in terms of dosing (less number of drops are necessary to achieve the intended dose with a higher concentration solution) and in terms of easiness of administration vis-à-vis tablets. Also, the onset of action may be 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 measures to avoid the risk of overdose in children, including contraindication in this patient population.

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

In its July 2013 opinion, the CHMP recommended that for all indications in adults the single dose 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, 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.

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. The CHMP considered that formulations with concentration 1mg/ml are suitable for those patients that may prefer an oral liquid formulation to a solid pharmaceutical form.

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 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.

Benefit–risk balance

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.

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

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.