The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION

PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Motilium and associated names

International NonProprietary Name (INN): domperidone

BACKGROUND INFORMATION

Domperidone is a peripheral dopamine D_2-receptor antagonist with gastrokinetic and anti-emetic properties. It is used in the treatment of symptoms of nausea and vomiting of variable origin. It exerts its actions via inhibition of dopamine receptors in the human gut, and in the chemoreceptor trigger zone (CTZ), which lies outside the blood-brain barrier in the area postrema. The active substance is available as domperidone and as domperidone maleate.

From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. On 31 October 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC[1].

The referral procedure started on 31 May 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of domperidone is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 27 June 2002, recommending the harmonisation of the SPC for Motilium and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 17 October 2002.

[1] Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Motilium and Associated names

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications.
For the majority of the European Union Member States, the approved indications for Motilium are treatment of nausea and vomiting and treatment of the symptoms of dyspepsia, however there was a disharmony in the labelling relating to;

- The indication "for up to 12 weeks treatment of nausea and vomiting caused by L-dopa and bromocriptine" exists in the UK, but this is not approved in France.
- The indication of "gastro-oesophageal reflux disease" is approved in France whereas this indication does not exist in UK.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Motilium, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications
Adults
The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

Children

The relief of the symptoms of nausea and vomiting.

Section 4.2. Posology and method of administration
The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to recommendations in the treatment of nausea and vomiting where the maximum dosage varies across EU states.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Motilium the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration
It is recommended to take oral Motilium before meals. If taken after meals, absorption of the drug is somewhat delayed.

The initial duration of treatment is four weeks. Patients should be re-evaluated after four weeks and the need for continued treatment re-assessed.

Adults and adolescents (over 12 years and weighing 35 kg or more)

- Tablets

1 to 2 of the 10-mg tablets three to four times per day with a maximum daily dose of 80 mg.

- Oral suspension

  10 mL to 20 mL (of oral suspension containing domperidone 1mg per mL) three to four times per day with a maximum daily dose of 80 mL.

- Effervescent granules

  1 to 2 sachets (containing domperidone 10 mg per sachet) three to four times per day with a maximum daily dose of 8 sachets.

- Suppositories

  60-mg suppositories two times per day.

Infants and children

- Tablets, Oral Suspension

  0.25 – 0.5 mg/kg three to four times per day with a maximum daily dose of 2.4 mg/kg (but do not exceed 80 mg per day).

  Tablets are unsuitable for use in children weighing less than 35 kg.

- Suppositories

  The total daily dose is dependent on the child's weight:

  For a child weighing 5-15 kg: 10-mg suppositories two times per day.

  For a child weighing more than 15 kg: 30-mg suppositories two times per day.

  Suppositories are unsuitable for use in children weighing less than 5 kg.

- Safety issues

Section 4.3. Contra-indications

The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to:

- History of iatrogenic dyskinesia
- Prolactinaemia
- Patients at risk of gastrointestinal haemorrhages, mechanic obstruction, digestive perforation due to hyperstimulation of gastrointestinal motility.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Motilium, the most suitable harmonised Section 4.3 Contraindications text was approved (See Annex). The text approved in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Motilium, the most suitable harmonised Section 4.4

Special Warnings and Precautions for Use text was approved (See Annex). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations
Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Motilium is favourable for use relating to relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The major divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time.

It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Motilium and associated names – see Annex I> <strength> <pharmaceutical form>.

(To be implemented nationally)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains domperidone 10 mg.

One film-coated tablet contains domperidone 10 mg.

Effervescent granules contain domperidone 10 mg per sachet.

The oral suspension contains domperidone 1 mg per ml.

One suppository contains domperidone 10 mg, 30 mg or 60 mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets - white to faintly cream coloured, circular, biconvex tablets

Effervescent granules - white granular powder with characteristic odour and flavour

Oral suspension - white homogenous suspension

Oral Lyophilisate - white to off white, circular, freeze dried units

Suppositories - white to slightly yellow suppositories

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

Children

- The relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

It is recommended to take oral Motilium before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents (over 12 years and weighing 35 kg or more)

The initial duration of treatment is four weeks. Patients should be re-evaluated after four weeks and the need for continued treatment re-assessed.

- Tablets

  1 to 2 of the 10-mg tablets three to four times per day with a maximum daily dose of 80 mg.

- Oral suspension

  10 mL to 20 mL (of oral suspension containing domperidone 1mg per mL) three to four times per day with a maximum daily dose of 80 mL.

- Effervescent granules

  1 to 2 sachets (containing domperidone 10 mg per sachet) three to four times per day with a maximum daily dose of 8 sachets.

- Suppositories

  60-mg suppositories two times per day.

Infants and children

- Tablets, Oral Suspension

  0.25 – 0.5 mg/kg three to four times per day with a maximum daily dose of 2.4 mg/kg (but do not exceed 80 mg per day).

  Tablets are unsuitable for use in children weighing less than 35 kg.

- Suppositories

  The total daily dose is dependent on the child's weight:

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  For a child weighing more than 15 kg: 30-mg suppositories two times per day.

  Suppositories are unsuitable for use in children weighing less than 5 kg.

4.3 Contraindications

Motilium is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).

Motilium should not be used when stimulation of the gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and special precautions for use

Precautions for use

The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption.
The oral suspension contains sorbitol and may be unsuitable for patients with sorbitol intolerance.
The effervescent granules contain fructose and may be unsuitable for patients with fructose intolerance.

Use in patients with risk of hyperphenylalaninaemia
The effervescent granules contain aspartame. Do not use in patients with a risk of hyperphenylalaninaemia.

Use during lactation
The total amount of domperidone excreted in human breast milk is expected to be less than 7µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking Motilium.

Use in infants:
Neurological side effects are rare (see "Undesirable effects" section). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Therefore, it is recommended that the dose be determined accurately and followed strictly in neonates, infants, toddlers and small children.

Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Use in liver disorders:
Since domperidone is highly metabolised in the liver, Motilium should be not be used in patients with hepatic impairment.

Renal insufficiency:
In patients with severe renal insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6 m mol/L) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

4.5 Interaction with other medicinal products and other forms of interaction

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. *In vivo* interaction studies with ketoconazole revealed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by ketoconazole.

4.6 Pregnancy and lactation

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, Motilium should only be used during pregnancy when justified by the anticipated therapeutic benefit.

The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/mL after oral and i.v. administration of 2.5 mg/kg respectively). Domperidone concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations and expected not to exceed 10ng/ml. The total amount of domperidone excreted in human breast milk is expected to be less than 7µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking Motilium.

4.7 Effects on ability to drive and use machines

Motilium has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

- *Immune System Disorder:* Very rare; Allergic reaction
- *Endocrine disorder:* Rare; increased prolactin levels
- *Nervous system disorders:* Very rare; extrapyramidal side effects
- *Gastrointestinal disorders:* Rare; gastro-intestinal disorders, including very rare transient intestinal cramps
- *Skin and subcutaneous tissue disorders:* Very rare; urticaria
- *Reproductive system and breast disorders:* Rare; galactorrhoea, gynaecomastia, amenorrhea

As the hypophysis is outside the blood brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea.

Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped.

4.9 Overdose

Symptoms
Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions, especially in children.

Treatment
There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacokinetic properties

Absorption
In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant

administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

After rectal administration of 60mg domperidone suppositories, a plateau is attained with domperidone plasma concentrations of about 20ng/ml lasting from 1 to 5 hours after administration. Although peak plasma levels are only about one third of that of an oral dose, the mean rectal bioavailability of 12.4% is quite similar to that after oral administration.

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

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

Excretion
Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

5.3 Preclinical safety data

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

(to be implemented nationally)

6.2 Incompatibilities

(to be implemented nationally)

6.3 Shelf life

(to be implemented nationally)

6.4 Special precautions for storage

(to be implemented nationally)

6.5 Nature and contents of container

(See Annex I - to be implemented nationally)

6.6 Instructions for use and handling

(to be implemented nationally)

7. MARKETING AUTHORISATION HOLDER

(See Annex I - to be implemented nationally)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT