

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Domperidon Actavis 10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 12.72 mg of domperidone maleate equivalent to 10 mg of domperidone.

Excipient: lactose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, circular, biconvex tablet with inscription "DM10" at one side.

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.

Adolescents over 12 years and weighing 35 kg or more

- The relief of symptoms of nausea and vomiting.

4.2 Posology and method of administration

For oral administration

It is recommended to take oral Domperidon Actavis 10 mg tablets 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

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

Infants and children

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. (See section 4.4)

4.3 Contraindications

Domperidon Actavis 10 mg tablets are contraindicated in the following situations:

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

Domperidon Actavis 10 mg tablets 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 precautions for use

Precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Domperidon Actavis 10 mg tablets are not recommended in breast-feeding women.

Use in infants

Neurological adverse events are rare (see section 4.8). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological adverse events 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.

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

Use in liver disorders:

Since domperidone is highly metabolised in the liver, Domperidon Actavis 10 mg tablets should 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 mmol/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.

Use with Ketoconazole

A slight increase of QT interval (mean less than 10msec) was reported in a drug-drug interaction study with *oral* ketoconazole. Even if the significance of this study is not fully clear, alternative therapeutic options should be considered if antifungal treatment is required. (See also sections 4.5)

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.

A *pharmacokinetic* study has demonstrated that the AUC and the peak plasma concentration of domperidone is increased by a factor 3 when *oral* ketoconazole is administered concomitantly (at steady state). A slight QT-prolonging effect (mean less than 10msec) of this combination was detected, which was greater than the one seen with ketoconazole alone.

A QT prolonging effect could not be detected when domperidone was given alone in patients with no co-morbidity, even at high oral doses (up to 160mg/day).

The results of this interaction study should be taken into account when prescribing domperidone concomitantly with strong CYP3A4 inhibitors: for example: ketoconazole, ritonavir and erythromycin (See also section 5.2).

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, Domperidon Actavis 10 mg tablets 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 Domperidon Actavis 10 mg tablets are not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines

Domperidon Actavis 10 mg tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequencies of adverse reactions are ranked according to the following:
very common (>1/10), common (>1/100, < 1/10);
uncommon (> 1/ 1,000, < 1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Immune system disorders:

Very rare; Allergic reactions including anaphylaxis, anaphylactic shock, anaphylactic reaction, urticaria and angioedema.

Endocrine disorders:

Rare; increased prolactin levels

Nervous system disorders:

Very rare; extrapyramidal adverse reactions

Gastrointestinal disorders:

Rare; gastro-intestinal disorders, including very rare transient intestinal cramps.

Very rare; diarrhoea

Skin and subcutaneous tissue disorders:

Very rare; pruritus, rash

Reproductive system and breast disorders:

Rare; galactorrhoea, gynaecomastia, amenorrhoea

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 reactions such as galactorrhoea, gynaecomastia and amenorrhoea.

Extrapyramidal adverse reactions are very rare in neonates and infants, and exceptional in adults. These adverse reactions 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 adverse events 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 oesophageal 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.

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

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in vitro* experiments on isolated cells transfected with HERG and on isolated guinea pig myocytes, ratios were about 10, based on IC50 values inhibiting currents through ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 20 mg (q.i.d.). However, safety margins in *in vitro* experiments on isolated cardiac tissues and in *in vivo* models (dog, guinea pig, rabbits sensitised for torsades de points) exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d.) by more than 50-fold. In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 10- fold.

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

Lactose monohydrate,
maize starch,
povidone K 30(E1201),
sodium laurylsulphate,
microcrystalline cellulose (E460),
colloidal silica anhydrate (E551)
magnesium stearate (E470B).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Transparent PVC/Al blister containing 10 tablets.
Pack sizes: 10, 20, 30, 50 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Group Hf.
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8. MARKETING AUTHORISATION NUMBERS

MA 651/00301.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14th December 2006

10. DATE OF REVISION OF THE TEXT