SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Domperidone Tablets, 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Domeridone BP..... 10 mg

Excipients..... q.s.

3. PHARMACEUTICAL FORM

Tablet

Light blue coloured, smooth, round, flat, beveled edged, uncoated tablets with breakline on side and plain on other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults: The relief of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

Children: The relief of symptoms of nausea and vomiting

4.2 Posology and method of administration

For oral administration.

It is recommended to take domperidone 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 35kg or more)

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

Children

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

4.3 Contraindications

Domperidone is contraindicated in the following situations:

Known hypersensitivity to domperidone or any of the excipients.

Prolactin-releasing pituitary tumour (prolactinoma.)

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

4.4 Special warnings and 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.

Use during lactation

The total amount of domperidone excreted in human breast milk is expected to be less than 7 micrograms 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 domperidone.

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 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, domperidone 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.

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 section 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 of 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, domperidone 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 800ng/ml after oral and i.v administration of 2.5mg/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 7micrograms 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 domperidone.

4.7 Effects on ability to drive and use machines

Domperidone has no or negligible influence on the ability to drive or 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.
- Gastro-intestinal 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, 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-endrocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are exceptional in adults. These side effects reverse spontaneously and completely as soon as 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 extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A03

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 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.

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.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch BP, Lactose, Sodium benzoate, Starch for paste, Purified water, Magnesium stearate, Colour Brilliant Blue Lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store between 15°C-30°C. Protect from light.

6.5 Nature and contents of container

Blister of 50 tablets, such two blisters are packed in a carton to give pack size of 2 x 50 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Cadila Pharmaceuticals Limited,

1389, Trasad Road, Dholka- 382 225,

District: Ahmedabad, Gujarat State, India.

8. MARKETING AUTHORISATION NUMBER(S)

CAD/IND/051
04451/06921/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/01/2015/
Apr 29, 2019

10. DATE OF REVISION OF THE TEXT

November 2016