For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

DOMSTAL DT

(Domperidone dispersible 5mg and10 mg tablet)

COMPOSITION

DOMSTAL – 5 DT

Each uncoated dispersible tablet contains :

Domperidone I.P. …..5mg

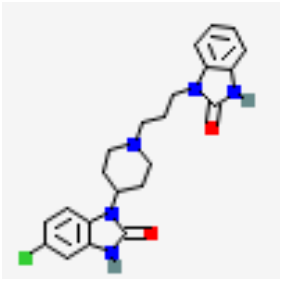
DOMSTAL – 10 DT

Each uncoated dispersible tablet contains :

Domperidone I.P. …..10mg

PROPERTIES

Domperidone is a dopamine antagonist with anti-emetic properties. Chemically it is 5-Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one. It has an empirical formula of $C_{22}H_{24}ClN_5O_2$ and molecular weight of 425.9. The structure is as follow



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially 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.

PHARMACOKINETICS

Absorption

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 domperidone is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or to induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins.

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.

INDICATIONS

For the relief of post-prandial symptoms of fullness, nausea, epigastric bloating and belching that is occasionally accompanied by epigastric discomfort and heartburn.

For the relief of nausea and vomiting of less than 48 hours duration.

CONTRAINDICATIONS

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- Hepatic and/or renal impairment

WARNING AND PRECAUTIONS:

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 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 domperidone.

Use in infants:

Neurological side effects are rare. 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, domperidon tablet 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 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 Potent CYP3A4 Inhibitors:

Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

PREGNANCY &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 tablet 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 domperidone.

Effects on Ability to Drive and Use Machines

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

ADVERSE EFFECTS

At the dosages and duration recommended here domperidone is generally very well tolerated with few undesirable effects.

The adverse drug reactions are ranked below by frequency, using the following convention: 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 disorder: Very rare; allergic reactions including anaphylaxis, anaphylactic shock, anaphylactic reaction and angioedema.

Psychiatric system disorders: Very rare: agitation, nervousness.

Endocrine disorder: Rare; increased prolactin levels.

Nervous system disorders: Very rare; extrapyramidal side effects, convulsion, somnolence, headache.

Cardiac disorders: QTc prolongation (frequency not known). Very rare: ventricular arrhythmias.

Gastrointestinal disorders: Rare; gastrointestinal disorders, including very rare transient intestinal cramps. Very rare: diarrhoea.

Skin and subcutaneous tissue disorders: Very rare; urticaria, pruritus, rash.

Reproductive system and breast disorders: Rare; galactorrhoea, gynaecomastia, amenorrhoea.

Investigations: Very rare: liver function test abnormal.

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 exceptional in adults. These side effects reverse spontaneously and completely as soon as treatment is stopped.

Other central nervous system-related effects of convulsion, agitation, and somnolence also are very rare and primarily reported in infants and children.

DRUG INTERACTIONS

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.

Separate *in vivo* pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3 A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec.

With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies.

In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200 mg twice daily) and erythromycin monotherapy (500 mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

DOSAGE AND METHOD OF ADMINISTRATION

The tablet should be dispersed in a teaspoonful of water before administration.

For the relief of symptoms of post prandial stomach discomfort

Adults and children 16 years of age and older:

Up to 10mg three times daily and at night. Maximum duration of course of treatment 2 weeks.

For the relief of nausea and vomiting

Adults and children 16 years of age and older:

Up to 10mg three times daily and at night. Maximum duration of course of treatment 48 hours.

Use in children under 16 years of age:

Not recommended.

OVERDOSE AND ITS TREATMENT

Symptoms. Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, disorientation, somnolence and extrapyramidal reactions.

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

Expiry date

Do not use later than date of expiry.

Storage

Store at a temperature not exceeding 30°C, protected from light and moisture.

Presentation

DOMSTAL – 5 DT & DOMSTAL - 10 DT are available in strip pack of 10 Tablets

Direction for use

Disperse the tablet in a teaspoonful of water before administration.

MARKETED BY

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