Domperidone

GI Norm®

10 mg Film-Coated Tablet

Rx

GASTROKINETIC / ANTIEMETIC

FORMULATION
Each film-coated tablet contains:
Domperidone ……..…… 10 mg

PRODUCT DESCRIPTION
Domperidone (GI Norm®) 10 mg Tablet is a white, round, biconvex, film-coated tablet plain on both sides.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Domperidone is a dopamine antagonist with antiemetic properties. It does not readily cross the blood-brain barrier. Domperidone seldom causes extrapyramidal effects, but it causes a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema.

Studies in humans have shown oral domperidone to increase lower esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. Domperidone has no effect on gastric secretion.

Pharmacokinetics
Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations (C_{max}) occurring at approximately 30 to 60 minutes after dosing in fasted individuals. The C_{max} and area under the curve (AUC) values of domperidone increase proportionally with dose in the 10 to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times a day (every 5 hours) dosing of domperidone for 4 days.

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 gastrointestinal complaints should take domperidone 15 to 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.

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 approximately 91 to 93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution but low brain concentration. Small amounts of the drug cross the placenta in rats.

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation.

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

Special Populations:

Hepatic Impairment: In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on C_{max} and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied.

Renal Impairment: In subjects with severe renal insufficiency (creatinine clearance <30mL/min/1.73m^2) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy volunteers. Very small amounts of unchanged drug (approximately 1%) are excreted via the kidneys.

Pediatric Patients: No pharmacokinetic data are available in the pediatric population.

INDICATION
• For the short-term treatment of nausea and vomiting

DOSAGE AND ADMINISTRATION
Domperidone should be used at the lowest effective dose for the shortest possible time.
Domperidone should be taken 15 to 30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.
The tablets must be swallowed whole with a glass of water. Do not crush or chew them.

Recommended dose for adults and adolescents 12 years and older weighing ≥35 kg: 1 tablet (10 mg) up to 3 times a day
Maximum dose in 24 hours: 30 mg
Or, as directed by a physcian.

Use in Renal Impairment: 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 of domperidone should be reduced to once or twice a day depending on the severity of the impairment. The dose may need to be reduced as well. Patients with renal impairment on prolonged domperidone therapy should be reviewed regularly.

- **The maximum treatment duration should not usually exceed one week.**
- Domperidone is unsuitable for use in children (less than 12 years old) and adolescents weighing less than 35 kg.

CONTRAINDICATIONS
- Hypersensitivity to domperidone or any ingredient in the product
- Prolactin-releasing pituitary tumor (prolactinoma)
- Patients with gastrointestinal hemorrhage, mechanical obstruction or perforation, or when stimulation of gastric motility could be harmful
- Patients with moderate or severe hepatic impairment
- Patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) or bradycardia; these are known to be conditions increasing the proarrythmic risk.
- Conditions where the cardiac conduction intervals are impaired or could be affected and underlying cardiac diseases as congestive heart failure, when co-administered with QT-prolonging drugs or potent CYP3A4 inhibitors **(see INTERACTIONS WITH OTHER MEDICAMENTS)**

WARNINGS AND PRECAUTIONS

Cardiovascular Effects
Domperidone has been associated with prolongation of the QT interval. During postmarketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Domperidone should be used with caution in older patients or those with current or history of cardiac disease. An increase in the risk of serious ventricular arrhythmias and sudden cardiac death has been reported in some epidemiology studies. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Treatment with domperidone should be discontinued if signs or symptoms occur that may be associated with cardiac arrhythmia. Patients should be advised to promptly report any cardiac symptoms to their physician.

Concomitant Use with Antacids or Secretory Agents

Antacids or antisecretory agents should not be taken simultaneously with domperidone since they lower the oral bioavailability of domperidone. When used concomitantly, domperidone should be taken before meals and antacids or antisecretory agents after meals.

Prolactin Levels

Domperidone produces an increase in plasma prolactin which persists with chronic administration but falls to normal upon discontinuation of the drug. During chronic oral administration of 30 mg daily for two weeks, the plasma prolactin level measured 90 minutes after medicine intake remained fairly constant at 25 ng/mL in males (normal value was 5 ng/mL), while in females, the level of 117 ng/mL after the first dose decreased to 56 ng/mL after 14 doses (pretreatment normal value was 9 ng/mL).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro,* a factor of potential importance if the administration of domperidone is contemplated in a patient with a past history of breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported with other prolactin-elevating medicines, the clinical significance of elevated serum prolactin levels is unknown. An increase in mammary neoplasms has been found in rodents after chronic administration of domperidone and other prolactin-stimulating medicines. Neither clinical studies nor epidemiological studies have shown an association between chronic administration of these medicines and mammary tumorigenesis. Domperidone does not affect plasma growth hormone or aldosterone levels.

Lactose Intolerance
This medicine contains lactose as one of its excipients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS WITH OTHER MEDICAMENTS
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.

Concomitant use of the following substances is contraindicated:
<u>QTc prolonging medicinal products</u>
- Class IA anti-arrhythmics (e.g., disopyramide, hydroquinidine, quinidine)
- Class III anti-arrhythmics (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- Certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- Certain antidepressants (e.g., citalopram, escitalopram)
- Certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- Certain antifungal agents (e.g., pentamidine)
- Certain antimalarial agents (in particular halofantrine, lumefantrine)
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- Certain antihistaminics (e.g., mequitazine, mizolastine)
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- Other medicines (e.g., bepridil, diphemanil, methadone)

<u>Potent CYP3A4 inhibitors (regardless of their QT prolonging effects)</u>
- HIV protease inhibitors (e.g., amprenavir, atazanavir, fosamprenavir, indinavir, ritonavir, saquinavir)
- Systemic azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- Some macrolides (erythromycin, clarithromycin, telithromycin)

Concomitant use of the following substances is not recommended:
- Calcium antagonists (e.g., diltiazem, verapamil)

Concomitant use of the following substances requires caution in use:
- Bradycardia- and hypokalemia-inducing drugs, as well as with macrolides involved in QT-interval prolongation, i.e., azithromycin and roxithromycin

The above list of substances is representative and not exhaustive.

Antacids or antisecretory agents lower the oral bioavailability of domperidone hence; they should not be given simultaneously.

Concomitant administration of anticholinergic drugs with domperidone may antagonize the anti-dyspeptic effect of domperidone.

Domperidone reduces the relaxant effect of atropine on the lower esophageal sphincter if given prior to atropine, but it has no reversing effect if atropine is administered first. Since domperidone has gastro-kinetic effects, it may influence the absorption of concomitantly administered oral medicines, particularly those of sustained-release or enteric-coated formulations.

If patients are already stabilized on digoxin, paracetamol or haloperidol, concomitant administration of domperidone does not influence the blood levels of these medicines.

Separate *in vivo pharmacokinetic/pharmacodynamic* interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first-pass metabolism by these drugs. The combination of oral domperidone 10 mg four times a day and ketoconazole 200 mg twice a day produced a mean QTc prolongation of 9.8 msec over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec.

STATEMENT OF USAGE IN HIGH-RISK GROUPS

Pregnancy
Pregnancy Category C. Limited postmarketing data exist on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential for toxicity in humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactation
The amount of domperidone that may be ingested by an infant through breast milk is extremely low. The maximal relative infant dose is estimated to be approximately 0.1% of the maternal weight-adjusted dose. Since it is not known whether this is harmful to the newborn, breastfeeding is not recommended for women taking domperidone.

Use in Children
Domperidone tablets are unsuitable for use in children weighing less than 35 kg. Although rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life.

Use in the Elderly
No special precautions are necessary in older patients.

UNDESIRABLE EFFECTS

General: Asthenia

Cardiovascular: Ventricular arrhythmias, sudden cardiac death, QTc prolongation, torsades de pointes

Central Nervous System: Somnolence, headache, convulsion, extrapyramidal disorder, depression, dizziness

Psychiatric: Loss of libido, anxiety, agitation, nervousness, akathisia

Gastrointestinal: Dry mouth, diarrhea

Immune System: Anaphylactic reaction including anaphylactic shock, hypersensitivity

Genitourinary: Urinary retention

Dermatologic: Rash, pruritus, urticaria, angioedema

Reproductive: Galactorrhea, breast pain, breast tenderness, gynecomastia, amenorrhea, irregular menstruation, breast swelling, lactation disorder

Special Senses: Oculogyric crisis

Investigations: Abnormal liver function test, increased blood prolactin

OVERDOSE AND TREATMENT

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

There is no specific antidote to domperidone overdose. In the event of an overdose, standard symptomatic treatment should be given immediately. Gastric lavage within one hour of ingestion as well as activated charcoal may be useful. Electrocardiogram (ECG) monitoring should be done due to the possibility of QT interval prolongation. Anticholinergics and anti-Parkinsonian agents may be helpful in controlling the extrapyramidal reactions.

STORAGE CONDITIONS
Store at temperatures not exceeding 30ºC.
Keep out of sight and reach of children.

AVAILABILITY
Domperidone (GI Norm®) 10 mg Film-coated Tablet in Blister foil pack of 10s (box of 100 tablets)

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at <u>www.fda.gov.ph</u> **AND** Unilab at (+632) 858-1000 or <u>productsafety@unilab.com.ph.</u> By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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