Size: 170 (L) x 240 (H) mm
Folding size: 30 x 60 mm
Carton size: 46 x 33 x 75 mm

Front

# DOMPERIDONE

## GASTRIUM™

10 mg Tablet
GASTROKINETIC

**PRODUCT NAME**
Gastrium

**DOSAGE FORM AND STRENGTH:**
Domperidone Tablets 10 mg

**PHARMACOLOGIC CATEGORY:** Gastrokinetic

**PRODUCT DESCRIPTION:**
Yellow coloured flat, circular, bevel edged, uncoated tablet with a breakline on one surface.

**FORMULATION/COMPOSITION:**
Each uncoated tablet contains:
Domperidone .....10 mg

**PHARMACODYNAMICS/PHARMACOKINETICS:**
***Pharmacodynamics:***
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 (gastro kinetic) 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.

***Pharmacokinetics:***
***Absorption***
Domperidone is rapidly absorbed after oral administration with peak plasma concentrations at approximately 1 hr after dosing. The Cmax and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) 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 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.

**INDICATIONS:**
Domperidone is indicated for the relief of the symptoms of nausea and vomiting.

**DOSAGE AND MODE/ROUTE OF ADMINISTRATION:**
For oral administration.
Domperidone tablets should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting
It is recommended to take oral domperidone tablets before meals. If taken after meals, absorption of the drug is somewhat delayed.
Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.
Usually, the maximum treatment duration should not exceed one week.
**Adults and adolescents (over 12 years and weighing 35kg or more)**
One 10mg tablet up to three times a day with a maximum dose of 30mg per day.
*Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg*
Due to the need for accurate dosing, tablets, effervescent granules and suppositories are unsuitable for use in children and adolescents weighing less than 35 kg.
*Hepatic Impairment*
Domperidone is contraindicated in moderate or severe hepatic impairment . Dose modification in mild hepatic impairment is however not needed.
*Renal Impairment*
Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

**CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)**
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.
- In patients with moderate or severe hepatic impairment.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac disease such as congestive heart failure.
- Co-administration with QT-prolonging drugs
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

Precautions for use
The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosemia or glucose/galactose malabsorption.
This medicinal product contains 0.97mmol (0.042mg) of sodium per tablet. To be taken into consideration by patients on a controlled sodium dose.
***Use in infants***
Although neurological side effects are 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.
Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.
***Renal impairment***
The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment., The dose may also need to be reduced. Such patients on prolonged therapy should be reviewed regularly.
***Cardiovascular effects:***
Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing 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.
Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. 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.
Domperidone should be used at the lowest effective dose in adults and children.
Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic risk.
Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.
Patients should be advised to promptly report any cardiac symptoms.

**PREGNANCY AND LACTATION:**

***Pregnancy***

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.

***Lactation***

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

**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 CYP3A4 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 the 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 (200mg twice daily) and erythromycin monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamics and/or pharmacokinetic interactions.

**Concomitant use of the following substances is contraindicated**

QTc-prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquindine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain antipsychotics (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 gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminic (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e : protease inhibitors

- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin and telithromycin)

**Concomitant use of the following substances is not recommended**

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

**Concomitant use of the following substances requires caution in use**

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

Opioids may antagonise the effects of domperidone on gastric emptying.

**ADVERSE DRUG REACTION:**

The adverse drug reactions are ranked below by frequency, using the following convention: very common (≥1/10), common (≥1/100, to <1/10); uncommon (≥ 1/1,000, to <1/100); rare (≥1/10,000, to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data).

- Immune System Disorder: Very rare; Allergic reaction, including anaphylaxis, anaphylactic shock, anaphylactic reaction and angiodema
- Endocrine disorder: Rare; increased prolactin levels
- Psychiatric system disorders: Very rare: agitation, nervousness.
- Nervous system disorders: Very rare; extrapyramidal side effects, convulsion, somnolence, headache, Not known; dystonia
- Eye disorders: Not known; Oculogyric crisis
- Cardiac disorders: Not known; Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, sudden cardiac death.
- Gastro-intestinal disorders: Rare gastro-intestinal disorders including very rare transient intestinal cramps, very rare; diarrhoea
- Skin and subcutaneous tissue disorders: Very rare; urticaria, pruritus, rashes
- Reproductive system and breast disorders: Uncommon: breast pain, Rare; Galactorrhea, gynaecomastia, amenorrhea, Not known; reduced libido.
- Investigations: very rare: liver function test abnormal.

As the hypothesis is outside the blood brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this Hyperprolactinemia may lead to neuro-Endocrinological side effects such as Galactorrhea, gynaecomastia and amenorrhea. 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.

**OVERDOSAGE AND TREATMENT:**

***Symptoms:*** Overdose has been reported primarily in infants and children. Symptoms of over dosage 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, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility pf QT prolongation. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling extrapyramidal reactions.

**STORAGE CONDITION:**

Store at a temperature not exceeding 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE:**

Alu/Clear PVC Blister foil of 10's (Box of 30's and 100's)

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):**

Not Applicable

**NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:**

**Marketing Authorization Holder**

Brown & Burk Philippines Inc
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

**NAME AND ADDRESS OF MANUFACTURER:**

**MICRO LABS LIMITED**
92, Sipcot Industrial Complex,
Hosur – 635 126 (T.N.), India.

**CAUTION STATEMENT:**

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

**ADR REPORTING STATEMENT**:

"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA:
www.fda.gov.ph
Seek medical attention immediately at the first sign of Adverse Drug Reaction.

**REGISTRATION NUMBER:**

DRP-586

**DATE OF FIRST AUTHORIZATION:**

12 Aug. 2008

**DATE OF REVISION OF PACKAGE INSERT:**

April 2018

EXG-ML12I-1991/A

| MICRO LABS LIMITED, BANGALORE, INDIA | | | |
|---|---|---|---|
| 1 | Product Name | Gastrium | Colours Used<br>BLACK |
| 2 | Strength | 10 mg | |
| 3 | Component | Leaflet | |
| 4 | Category | Export - Philippines | |
| 5 | Dimension | 170 x 240 mm | |
| 6 | Artwork Code | EXG-ML12I-1991/A | |
| 7 | Pharma Code | N/A | |
| 8 | Reason for Change | Text corrections from Customer | |

| | Prepared by (DTP) | Checked by (PD) | Approved by | | | |
|---|---|---|---|---|---|---|
| | | | Head CQA | Head Production/ Packing (Site) | Head QC (Site) | Head QA (Site) |
| Sign | Kantharaju L. | | | | | |
| Date | 17-07-2021 | | | | | |