PANTOPRAZOLE GASTRO RESISTANT TABLETS 40mg
PANTOMAC

NAME AND STRENGTH OF ACTIVE INGREDIENT:
Each gastro-resistant tablet contains:
Pantoprazole Sodium Sesquihydrate equivalent to Pantoprazole …..40mg

PRODUCT DESCRIPTION:
Yellow colored, enteric coated, oval biconvex tablets plain on both the side.

PHARMACOLOGY:
Pharmacodynamics:
Pantoprazole is substituted benzimidazoles which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, and gastrin). The effect is the same whether the product is given orally or intravenously.
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.
Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Pharmacokinetics:
Absorption:
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2 - 3 µg/ml are achieved, and these values remain constant after multiple administration.
Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.
The absolute bioavailability from the tablet was found to be about 77 %. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.
Distribution:
Pantoprazole's serum protein binding is about 98 %. Volume of distribution is about 0.15 l/kg.
Biotransformation:
The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation; other metabolic pathway includes oxidation by CYP3A4.
Elimination: Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).
Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole; the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.
Special populations
Poor metabolisers
After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in healthy subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.
***Renal impairment*:**
No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3 h), excretion is still rapid and thus accumulation does not occur.
Hepatic impairment:
Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.
***Older people*:** A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.
***Paediatric population*:** Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years AUC and C_{max} were in the range of corresponding values in adults.

INDICATIONS:
In combination with two appropriate antibiotics for the eradication of Helicobacter pylori in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe cases of inflammation of the esophagus (reflux esophagitis).
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

RECOMMENDED DOSE:
Pantoprazole gastro-resistant tablets 40 mg should not be chewed or crushed, and should be swallowed whole
1 hour before a meal. With some water
- **Recommended dose:**

Adults and adolescents 12 years of age and above:
Treatment of moderate and severe reflux oesophagitis
One tablet of Pantoprazole 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole 40mg daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.
Adults:
Eradication of H. pylori in combination with two appropriate antibiotics
In *Helicobacter pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of H. pylori:
a) 2 x 1 Pantoprazole 40mg gastro-resistant tablet/day
+ 2 x 1000 mg amoxycillin/day
+ 2 x 500mg clarithromycin /day
b) 2 x 1 Pantoprazole 40mg gastro-resistant tablet/day
+ 2 x 500 mg metronidazole/day
+ 2 x 500mg clarithromycin/day
c) 2 x 1 Pantoprazole 40mg gastro-resistant tablet/day
+ 2 x 1000 mg amoxycillin/day
+ 2 x 500mg metronidazole/day
In combination therapy for eradication of *H. pylori* infection, the second Pantoprazole tablet should betake 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.
If combination therapy is not an option, e.g. if the patient has tested negative for *Helicobacter pylori*, the following dosage guidelines apply for *Pantoprazole* monotherapy:
Treatment of gastric ulcer: One Pantoprazole 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole 40mg /daily) especially when there has been no response to other treatment. A 4 week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.
Treatment of duodenal ulcer: One tablet of Pantoprazole 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole 40mg daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.
Zollingen-Ellison-Syndrome and other pathological hyper secretory conditions
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions patients should start their treatment with a daily dose of 80 mg (2 tablets of Pantoprazole 40 mg). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.
Treatment duration in Zollingen-Ellison-Syndrome and other pathological hyper secretory conditions is not limited and should be adapted according to clinical needs.
Special populations: Children below 12 years of age: Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.
Hepatic impairment: A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment of these patients
Renal Impairment: No dose adjustment is necessary in patients with impaired renal function. Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment for these patients.
Elderly: No dose adjustment is necessary in elderly patients.

METHOD OF ADMINISTRATION
Oral use
The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

CONTRAINDICATIONS:
Hypersensitivity to the active substance, substituted benzimidazoles or to any of the other excipients

WARNINGS AND PRECAUTIONS:

Hepatic impairment: In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes, the treatment should be discontinued.

Combination therapy: In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

Gastric malignancy: Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of any alarm symptom (e. g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability.

Influence on vitamin B12 absorption: In patients with Zollinger-Ellison syndrome and other pathological hyper secretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Long term treatment: In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal infections caused by bacteria: Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Hypomagnesaemia: Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures: Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in older people or in the presence of other recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Sub acute cutaneous lupus erythematosus (SCLE): Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping Pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with Laboratory Tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Pantoprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Regular Surveillance

Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Clostridium Difficile Diarrhea

Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

Adverse drug reactions, such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICAMENTS:

Medicinal products with pH-Dependent Absorption Pharmacokinetics

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral availability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability.

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitors may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.
Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.
Other interactions studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.
Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.
An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.
Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol), or does not interfere with p-glycoprotein related absorption of digoxin.
There were no interactions with concomitantly administered antacids.
Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.
Medicinal products that inhibit or induce CYP2C19:
Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

PREGNANCY AND LACTATION:
Pregnancy: A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of Pantoprazole.
Animal studies have shown reproductive toxicity
As a precautionary measure, it is preferable to avoid the use of Pantoprazole during pregnancy.
Lactation: Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from Pantoprazole therapy taking into account the benefit of breast-feeding for the child, and the benefit of Pantoprazole therapy for the woman.
Fertility: There was no evidence of impaired fertility following the administration of pantoprazole in animal studies.

UNDESIRABLE EFFECTS:
Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of patients.
The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
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 the available data).
For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
System Organ Class					
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia. Hypocalcaemia(1) Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as

					the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Parasthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic Colitis
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity, Sub acute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		Muscle spasm[(2)]
Renal and urinary disorders					Interstitial Nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

[1.] Hypocalcaemia in association with hypomagnaesemia
[2.] Muscle spasm as a consequence of electrolyte disturbance

Clostridium Difficile Diarrhea
Infections & infestations: Clostridium difficile associated diarrhea.
Vitamin B12 Deficiency
Metabolic/Nutritional: Vitamin B12 deficiency

Effects on ability to drive and use machines
Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

OVERDOSAGE AND TREATMENT:
There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

STORAGE CONDITION:
Store below 30°C. Keep out of reach of children.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Dosage form: Tablets
Packaging: Blister pack of 7 x 14's pack.

Manufactured by:
MICRO LABS LIMITED
Plot No. S-155 to S-159 & N1,
Phase III & IV, Verna Industrial Estate,
Verna Salcette, GOA - 403 722, INDIA

Date of Revision of Package Insert: May.2020