120mm

180mm

GASTASID

(P a n t o p r a z o l e)

Enteric Coated Tablets
20 mg
40 mg

گیسٹیسڈ

۲۰ ملی گرام
۴۰ ملی گرام

GASTASID (Pantoprazole tablets, USP)

CLINICAL PARTICULARS
Therapeutic Indications
GASTASID is a proton pump inhibitor (PPI) indicated for the following:

- **Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)**

GASTASID is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of GASTASID may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.

- **Maintenance of Healing of Erosive Esophagitis**

GASTASID is indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and night time heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

- **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**

GASTASID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

- GASTASID is indicated for eradication of Helicobacter pylori (H. pylori) in combination with appropriate antibiotic therapy in patients with H. pylori associated ulcers.
- GASTASID is indicated for gastric and duodenal ulcer.

DOSAGE AND ADMINISTRATION
Recommended Dosing Schedule for GASTASID

Indication	Dose & Frequency
Short-Term Treatment of Erosive Esophagitis Associated with GERD	
Adults	40 mg once daily for up to 8 weeks*
Children (5 years and older)	
≥ 15 kg to < 40 kg	20 mg once daily for up to 8 weeks
≥ 40 kg	40 mg
Maintenance of Healing of Erosive Esophagitis	
Adults	40 mg once daily***
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	
Adults	40 mg twice daily**
Eradication of *H. pylori* in combination with two appropriate antibiotics	
Adults In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents.	Depending upon the resistance pattern, the following combinations can be recommended for the eradication of*H. pylori*: a) Twice daily 40mg Pantoprazole + twice daily 1000 mg amoxicillin + twice daily 500 mg clarithromycin b) Twice daily 40mg Pantoprazole + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole) + twice daily 250 - 500 mg clarithromycin c) Twice daily 40mg Pantoprazole + twice daily 1000 mg amoxicillin + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)
Treatment of gastric ulcer	
Adults	40mg Pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets of Pantoprazole 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	
Adults	40mg Pantoprazole per day. In individual cases the dose may be doubled (increase to 2 tablets of Pantoprazole 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.

* For adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of GASTASID may be considered.
** Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.
*** Controlled studies did not extend beyond 12 months

Hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

Renal impairment
No dose adjustment is necessary in patients with impaired renal function.

Elderly
No dose adjustment is necessary in elderly patients.

Paediatric population
Pantoprazole is indicated for the short term treatment of EE associated with GERD for patients 5 years and older.
The safety and effectiveness of Pantoprazole for pediatric uses other than EE have not been established.

Method of administration
The tablets 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 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 SMPCs 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, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded.

Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors such as atazanavir.

Influence on vitamin B12 absorption
In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria.

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. Pantoprazole, like all PPIs might increase the counts of bacteria normally present in the upper GIT.

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

Bone fractures
PPIs 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 the elderly or in presence of other recognised 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.
Subacute cutaneous lupus erythematosus (SCLE)
PPIs are associated with very infrequent cases of SCLE. If lesions occur, the patient should seek medical help promptly and the HCPs should consider stopping Pantoprazole.

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.

INTERACTIONS
Medicinal products with pH-dependent absorption pharmacokinetics
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 such as atazanavir due to significant reduction in their bioavailability. If the combination of HIV protease inhibitors with a PPI is unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded.

Coumarin anticoagulants (phenprocoumon or warfarin)
There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate
In settings where PPIs are used concomitantly with high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered due to increase methotrexate levels in some patients.

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. An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.
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.

Deputy Manager Q.O.	_____	Controller Medical Affairs	_____
Controller RA & NPD	_____	Director Marketing & Sales	_____
Sr. Manager Technical	_____	Head of Quality operation	_____
Product Manager	_____	Managing Director	_____
Business Unit Head	_____	Responsibilities:	
Sr. Manager Medical Affairs	_____	QA & QC: Regulatory aspects e.g., layout of artwork, composition, Reg. no, Mfg. Lic. no & spec, instructions, size etc R.A.: Verification of all regulatory aspects Marketing: Design, color scheme, pack size, strength, dosage, Medical text (leaflet) Medical: Dosage, Medical text (leaflet)	

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 BREAST FEEDING

Pregnancy

It is preferable to avoid the use of Pantoprazole during pregnancy, as animal studies have shown reproductive toxicity.

Breast-feeding

Animal studies have shown excretion of pantoprazole in breast milk. Pantoprazole therapy should be given after considering the risk benefits for breast feeding women.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

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

ADVERSE REACTIONS

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.

Table 1: Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia, Hypomagnesaemia, Hypocalcaemia in association with hypomagnesemia; Hypokalaemia
Psychiatridisorders		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 systemdisorders		Headache; Dizziness	Taste disorders		Paraesthesia
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			
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; Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders			Gynaecomastia		Interstitial nephritis (with possible progression to renal failure).
Reproductive system and breast disorders					
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

OVERDOSE

There are no known symptoms of overdose in man.

PHARMACOLOGICAL PROPERTIES

Mechanism of action

Pantoprazole is a substituted benzimidazole 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 PPIs and H2 receptor inhibitors, pantoprazole reduces acidity in the stomach and 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, gastrin).

Pharmacokinetic Properties

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 do 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 pathways include 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

Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. 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 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 - 3h), 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.

Elderly

A slight increase in AUC and Cmax 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 Cmax were in the range of corresponding values in adults. Following administration of single IV doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

STORAGE:

Do not store above 25°C.
Protect from light, moisture & heat.
Keep medicine out of the reach of children.

PRESENTATION:

GASTASID 20 mg Tablets (enteric coated) are available in 14's.
GASTASID 40 mg Tablets (enteric coated) are available in 14's.

خوراک وہدایات:

۲۰ ملی گرام: ایک ٹیبلیٹس روزانہ یا ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
۴۰ ملی گرام: ٹیبلیٹ روزانہ یا ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

25°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
روشنی، نمی اور گرمی سے بچائیں۔
دوا کو بچوں کی پہنچ سے دور رکھیں۔

40003529

AGP

Manufactured by:
AGP Limited
B-23-C, S.I.T.E., Karachi

Marketed by:
Aspin Pharma (Private) Limited
Plot No. 10 & 25, Sector 20, K.I.A., Karachi