For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

PANTAZ 40mg Tablets Pantoprazole Sodium

DOSAGE FORM

Oral- enteric coated tablets

NAME AND STRENGTH OF ACTIVE SUBSTANCES

Each tablet contains 45.20mg pantoprazole sodium sesquihydrate (corresponding to 40mg pantoprazole).

PRODUCT DESCRIPTION

Pantaz 40mg Tablets (Pantoprazole Sodium Tablets 40 mg): Yellow coloured, circular, biconvex, delayed release tablet having plain surface on the both sides.

PHARMCODYNAMICS

Pharmacotherapeutic / indication group / action mechanism

Selective proton pump inhibitor, substituted benzimidazole, ATC code: A02BC02

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 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, gastrin). The effect is the same whether the product is given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases.

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

After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (Cmax) of 1 to 1.5 µg/mL (pantoprazole 20 mg tablet) or 2 to 3 µg/mL (pantoprazole 40 mg tablet) are achieved at about 2 to 2.5 hours after administration. After single and repeated administration of pantoprazole, the pharmacokinetic characteristics of pantoprazole are very similar.

Both oral and I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no relevant influence either on the AUC or on the Cmax 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%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

Metabolism

Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver.

Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

Excretion and Elimination

About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the feces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. T1/2 of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

Special Populations

Impaired renal function

In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy subjects. No dose adjustment is necessary in patients with impaired renal function.

Impaired hepatic function

No accumulation following once-daily dosing.

Drug Interactions

Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out. Nevertheless, in specific tests pantoprazole did not affect the clearance of several

compounds metabolized by CYP enzymes. Vice-versa, all drugs in regards with their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.

Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) does not interfere with pglycoprotein related absorption of digoxin.

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 DOSAGE

The following information applies unless pantoprazole has been otherwise prescribed by your doctor. Please follow these instructions, as otherwise pantoprazole may not have the desired effect!

Adults and adolescents 12 years of age and above:

<u>Treatment of moderate and severe reflux oesophagitis</u>

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.

Adults:

<u>Eradication of H. pylori in combination with two appropriate antibiotics</u>

In cases of duodenal or gastric ulcer in which infection with Helicobacter pylori has been confirmed, the microorganism should be eradicated by combination treatment. Depending on the resistance pattern, the following combinations are recommended:

a) 2 x 1 Pantaz 40 mg gastro-resistant tablet / day

   + 2 x 1000 mg amoxicillin / day

   + 2 x 500 mg clarithromycin /day

b) 2 x 1 Pantaz 40 mg gastro-resistant tablet / day

   + 2 x 500 mg metronidazole / day

+ 2 x 500 mg clarithromycin / day

c) 2 x 1 Pantaz 40 mg gastro-resistant tablet / day

+ 2 x 1000 mg amoxicillin / day

+ 2 x 500 mg metronidazole / day

Treatment of gastric and 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.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 tablets of pantoprazole tablets 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 Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Children below 12 years of age:

Pantoprazole 40mg is not recommended for use in children below 12 years of age due to limited data in this age group.

Type and duration of treatment

Combination therapy for eradication of Helicobacter pylori infection usually lasts 7 days and can be extended to a maximum of 2 weeks. If after this time further treatment with Pantoprazole 40 mg is indicated to ensure that the ulcer heals completely, the dose recommendations for gastric and duodenal ulcers must be observed. In the majority of cases, a duodenal ulcer heals completely within 2 weeks. If a two-week treatment period is not sufficient, healing will be achieved in almost all cases within a further 2 weeks. Gastric ulcers and reflux esophagitis usually require a 4-week course of treatment. If this should be inadequate, healing will in most cases be achieved within a further 4 weeks. Treatment should not exceed 8 weeks as experience with long-term use is limited. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Instructions for use / handling

Pantoprazole 40mg tablets must not be chewed or crushed and must be swallowed whole with water. In combination therapy for eradication of Helicobacter pylori infection the second pantoprazole 40mg tablet should be taken before the evening meal.

Special Patient Populations

Impaired hepatic function:

A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole or half a vial of 40 mg pantoprazole I.V.) should not be exceeded in patients with severe liver impairment.

Impaired renal function:

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

ROUTE OF ADMINISTRATION

To be administered orally.

CONTRAINDICATIONS

Pantoprazole must not be used in combination treatment for eradication of Helicobacter pylori in patients with moderate to severe liver or kidney function disturbances. Pantoprazole should generally not be used in cases of known hypersensitivity to one of the constituents of pantoprazole or of the combination partners.

WARNINGS AND PRECAUTIONS

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

Subacute Cutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sunexposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Pantaz 40mg Tablets. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPI like Pantaz 40mg Tablets 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 PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Fracture
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 the elderly or in presence

of other recognised 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.

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.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, Pantaz 40mg Tablets treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). 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.

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.

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Gastric malignancy:

Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.

Pregnancy and lactation

The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

Effects on the ability to drive and to use machines

Pantoprazole is not expected to adversely affect the ability to drive or 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

Drugs with pH-Dependent Absorption Pharmacokinetics:

Pantoprazole may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability.

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Other interaction 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 which include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, including carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions.

An interaction of pantoprazole with other drugs 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 metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Clopidogrel:

No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine):

Concomitant administration of pantoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin):

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon 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.

UNDESIRABLE EFFECTS

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common; common; uncommon; rare; very rare, not known.

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.

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

Frequency / Organ System	Common	Uncommon	Rare	Very Rate	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; weight changes		Hyponatraemia; Hypomagnesaemia; Vitamin B12 Deficiency;

					Hypocalcaemia in association with hypomagnesemia; Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Nervous system disorders		Headache; Dizziness	Taste disorders		
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	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens- Johnson-Syndrome; Erythema multiforme; Lyell-Syndrome; Photosensitivity; Subacute cutaneous lupus erythematosus
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances

Renal and urinary disorders					Interstitial nephritis
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		
Infections & infestations					*Clostridium difficile* associated diarrhea

OVERDOSAGE AND TREATMENT

Systemic exposure with up to 240 mg administered intravenously over 2 minutes is well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialyzable.

In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

STORAGE CONDITIONS

Store at temperature not exceeding 30°C, in a dry place.

PRESENTATION

A Carton containing 10 Alu-Alu blisters of 10 tablets.
A Carton containing 1 Alu-Alu blister of 14 tablets.

MANUFACTURED BY:

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PRODUCT REGISTRATION HOLDER

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