



APO-PANTOPRAZOLE

Pantoprazole 20mg and 40mg enteric coated tablets

Presentation

Apo-PANTOPRAZOLE 20 mg tablets are yellow, oval, biconvex, film-coated tablets, engraved "APO" on one side and "P20" on the other side.

They contain pantoprazole sodium sesquihydrate as the active ingredient, equivalent to 20 mg pantoprazole.

Apo-PANTOPRAZOLE 40 mg tablets are yellow, oval, biconvex, film-coated tablets, engraved "APO" on one side and "P40" on the other side.

They contain pantoprazole sodium sesquihydrate as the active ingredient, equivalent to 40 mg pantoprazole.

Other ingredients in Apo-Pantoprazole are anhydrous lactose, methacrylic acid copolymer, hypromellose, microcrystalline cellulose, titanium dioxide, crospovidone, purified talc, triethyl citrate, macrogol 8000, magnesium stearate, anhydrous sodium carbonate and iron oxide yellow.

Uses

Actions

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic canaliculi of the parietal cells when 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 in two weeks. As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in 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, the substance can affect 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 normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments can be ruled out for humans for a one-year treatment period.

An influence of a long-term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.



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Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after a single oral dose. On average, at about 2.0–2.5 h post administration, the maximum serum concentrations of about 1–1.5 µg/mL (pantoprazole 20 mg) and 2–3 µg/mL (pantoprazole 40 mg) are achieved, and these values remain constant after multiple administration.

Volume of distribution is about 0.15 L/kg and clearance is about 0.1 L/h/kg. Terminal half-life is about one hour. 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).

Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole is virtually linear after both oral and intravenous administration.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulfate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces.

Bioavailability

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability from tablets is about 77%. Concomitant intake of food has no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Characteristics in Patients/Special Groups of Subjects

No dose reduction is required when pantoprazole is administered to patients with restricted kidney function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialysed. Although the main metabolite has a moderately delayed half-life (2–3 h), excretion is still rapid and thus accumulation does not occur.

For patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3–6 h (pantoprazole 20 mg) and 7–9 h (pantoprazole 40 mg), and the AUC values increased by a factor of 3–5 (pantoprazole 20 mg) and between 5–7 (pantoprazole 40 mg). However, the maximum serum concentration only increased slightly by a factor of 1.3 (pantoprazole 20 mg) and 1.5 (pantoprazole 40 mg) compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.



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Indications

1. For the symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)
 - Reflux oesophagitis
 - Zollinger-Ellison Syndrome
2. Eradication of *Helicobacter pylori* (hereinafter referred to as *H. pylori*) in combination with:
 - clarithromycin and amoxicillin or
 - clarithromycin and metronidazole or
 - amoxicillin and metronidazole(see **Dosage and Administration**) in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.

The NIH has recommended that regimens to eradicate *H. pylori* in patients with PUD should contain both anti-secretory agents and anti-microbial agents (to which *H. pylori* has been demonstrated to be sensitive *in vivo*). A trial by Bardhan in patients with gastritis, florid duodenal ulcer or history of duodenal ulcer has demonstrated that pantoprazole 40 mg twice daily in the combination with tinidazole 500 mg twice daily and clarithromycin 250 mg twice daily for 10 days is effective in eradicating *H. pylori* in 86% of cases. Following combination therapy the DU healing rate was 100% after one month.
3. Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

Maintenance

Pantoprazole is indicated for maintenance treatment of reflux oesophagitis, duodenal ulcer, gastric ulcer and Zollinger-Ellison syndrome. Prolonged treatment should be considered:

- in patients who have recurrent peptic ulceration where the pathogenesis of the ulcer is not related to *H. pylori* infection; or
- where repeated eradication therapy is unsuccessful; or
- in patients who have a past history of perforation or bleeding from an ulcer.



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Dosage and Administration

H. pylori Eradication

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective.

1. twice daily, one 40 mg pantoprazole tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin
2. twice daily, one 40 mg pantoprazole tablet
+ twice daily 500 mg metronidazole
+ twice daily 500 mg clarithromycin
3. twice daily, one 40 mg pantoprazole tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg metronidazole

In the case of combination therapy the datasheets of the respective drugs should be observed.

Combination therapy involving metronidazole must only be used if the other combination partners are contraindicated, since damage to human germ cells by metronidazole cannot be excluded and animal studies revealed an increased incidence of certain tumours.

General Instructions

Pantoprazole tablets should not be chewed or crushed, and should be swallowed whole with some liquid. For eradication of *H. pylori*, convenient dosing could be at breakfast and dinner times. The combination therapy is implemented for 7 days. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dosage 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 *H. pylori*, the following dosage guidelines apply for pantoprazole monotherapy:

Duodenal Ulcer

The recommended oral dosage is one 40 mg pantoprazole tablet *per day*.

A duodenal ulcer generally heals within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

Gastric Ulcer

The recommended oral dosage is one 40 mg pantoprazole tablet *per day*.

A four-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further four weeks.



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GORD

For **mild reflux disease and the associated symptoms**, the recommended dosage is one 20 mg pantoprazole tablet *per day*.

Symptom relief is generally accomplished within 2–4 weeks. If symptom control has not been achieved after four weeks treatment with pantoprazole 20 mg tablets daily, further investigation is recommended.

For treatment of **reflux oesophagitis**, the recommended oral dosage is one 40 mg pantoprazole tablet *per day*.

A four-week period is usually required for treatment of reflux oesophagitis; however if this is not sufficient, healing will usually be achieved within a further four weeks.

Zollinger-Ellison Syndrome

The recommended oral dosage is one 40 mg pantoprazole tablet *per day*.

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dosage is one 20 mg pantoprazole tablet *per day*.

Maintenance

Duodenal & Gastric Ulcer and Zollinger-Ellison Syndrome:

For long-term management, a maintenance dose of one gastro-resistant tablet pantoprazole 40 mg *per day* is recommended.

Reflux Oesophagitis

A maintenance dose of one 20 mg pantoprazole tablet *per day* is recommended, increasing to 40 mg *per day* if relapse occurs. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Experience with long-term administration in man over several years is available in a limited number of patients. Therefore, long-term treatment exceeding one year may be considered after careful evaluation of the risk benefit ratio. Patients should then be kept under regular surveillance.

Use in Children

There are no data currently available on the use of pantoprazole in children.

Use in the Elderly

The daily dose of 20 mg or 40 mg can be given. An exception is combination therapy for eradication of *H. pylori*, where elderly patients should also receive the usual pantoprazole dose (2 × 40 mg/day) during one-week treatment.

Impaired Renal Function

The daily dose of 20 mg or 40 mg can be given.

Impaired Liver Function



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In patients with severe liver impairment the dose has to be reduced to 20 mg pantoprazole *per* day.

Contraindications

Apo-Pantoprazole should generally not be used in cases of known hypersensitivity to one of the constituents of the tablets or of the combination partners.

Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see **Interactions**).

Warnings and Precautions

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, pantoprazole should be discontinued.

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, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

The use of pantoprazole 20 mg as a preventive of gastroduodenal ulcers induced by NSAIDs should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (> 65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Generally, daily treatment with any acid-blocking medicines over a long time (e.g. longer than three years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered if respective clinical symptoms are observed.

To date there has been no experience with treatment in children.

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

Patients being treated for mild reflux disease and associated symptoms with pantoprazole 20 mg, who do not respond after four weeks, should be investigated.

In the case of combination therapy the data sheets of the respective drugs should be observed.



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Use in Pregnancy and Lactation

Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight foetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.

Effects on Ability to Drive and Use Machines

There are no known effects on the ability to drive and use machines.

Adverse Effects

Very common	(≥ 10%)
Common	(≥ 1% – < 10%)
Uncommon	(≥ 0.1% – < 1%)
Rare	(≥ 0.01% – < 0.1%)
Very rare	(< 0.01%)

Gastrointestinal disorders

Common: gastrointestinal complaints such as upper abdominal pain, diarrhoea, constipation or flatulence.

Uncommon: nausea, vomiting.

Rare: dry mouth.

General disorders and administration site conditions

Very rare: peripheral oedema.

Hepatobiliary disorders

Very rare: severe hepatocellular damage leading to jaundice with or without hepatic failure.

Immune system disorders

Very rare: anaphylactic reactions including anaphylactic shock.

Investigations:

Very rare: increased liver enzymes (transaminases, γ -GT), elevated triglycerides, increased body temperature.

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia.

Very rare: myalgia.



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Nervous system disorders

Common: headache.

Uncommon: dizziness, disturbances in vision (blurred vision).

Psychiatric disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Renal and urinary disorders

Very rare: interstitial nephritis.

Skin and subcutaneous tissue disorders

Uncommon: allergic reactions such as pruritus and skin rash.

Very rare: urticaria; angioedema; severe skin reactions such as Stevens-Johnson Syndrome, erythema multiforme, Lyell-Syndrome; photosensitivity.

Blood and lymphatic system disorders

Very rare: leukopenia, thrombocytopenia.

Interactions

Pantoprazole may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely antipyrine, carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalized ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore, proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see **Contraindications**).



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Overdosage

There are no known symptoms of overdosage in man.

Doses up to 240 mg i.v. were administered over two minutes and were well tolerated.

In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

Contact the Poisons Information Centre for advice on the management of an overdose.

Pharmaceutical Precautions

Storage conditions: store below 25°C.

Shelf life: 18 months.

Medicine Classification

Prescription Medicine

Package Quantities

Blister packs of 30 tablets.

Bottles of 30, 100, 500 or 1000 tablets.

Further Information

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In a two-year carcinogenicity study (corresponding to lifetime treatment) in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic treatment.

In the two-year studies an increased number of liver tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.



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Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

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