For the use of a Registered Medical Practitioner/ Hospital/ Laboratory Only

Pantoprazole Tablets IP

Pantopax™ 40

TABLETS

COMPOSITION:
Each enteric coated tablet contains:
Pantoprazole Sodium IP
Equivalent to Pantoprazole 40 mg
Excipients q.s.
Colours: Yellow Oxide of Iron & Titanium Dioxide IP

PHARMACEUTICAL FORM
Enteric Coated Tablet.

THERAPEUTIC INDICATION
Indicated for the treatment of gastric ulcer, duodenal ulcer & Gastroesophageal reflux disease (GERD).

DOSAGE AND ADMINISTRATION
The recommended adult dosage of Pantoprazole is 1 tablet (40mg) once daily or as directed by the Physician.
Method of administration: For oral administration only.
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, any of the other excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
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.
Combination therapy: In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.
Co-administration with HIV protease inhibitors: The 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 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.
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.

DRUG INTERACTION
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 inhibtors: 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 20mg 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.
Methotrexate: Concomitant use of high dose methotrexate (e.g. 300mg) 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.
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.

USE IN SPECIAL POPULATION
Elderly: No dose adjustment is necessary in older people. 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 40mg pantoprazole to children aged 5-16 years AUC and Cmax were in the range of corresponding values in adults. AUC and volume of distribution were in accordance with data from adults. Pantoprazole is not recommended for use in children below 12 years of age because of limited data on safety and efficacy in the age group.
Patients with 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.
Patients with renal impairment: No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). 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.
Pregnancy: A moderate amount of data on the 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.
Breast-feeding: 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 with pantoprazole in animal studies.

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.

UNDESIRABLE EFFECTS
Proton Pump Inhibitors associated Acute Kidney Injury : Acute kidney injury has been reported with the use of Proton pump inhibitors (PPIs) including Pantoprazole, Omeprazole, Lansoperazole, Esomeprazole, Rabeprazole etc.
The most frequently occurring adverse reactions, occurring at a rate of > 2% , in patients on oral pantoprazole (20mg or 40 mg) were headache, diarrhea, nausea, abdominal pain, vomiting flatulence, dizziness and arthralgia. Additional adverse reaction that were reported for pantoprazole with a frequency of <2% were allergic reaction, pyrexia, photosensitivity reaction, facial edema, constipation, dry, mouth hepatitis, leucopenia, thrombocytopenia, elevated CK (creatine kinese) generalized edema, elevated triglycerides, elevated liver enzymes, myalgia, depression, vertigo, urticaria, rash pruitus and blurred vision.
In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions included URI, Headache, fever, diarrhea, vomiting, rash and abdominal pain.
Additional adverse reactions reported for pantoprazole in pediatric patients with frequency of < 4% were allergic reaction, facial edema, constipation, flatulence, nausea, elevated triglycerides, elevated liver enzymes, elevated CK (creatine kinase), arthralgia, myalgia, dizziness, vertigo and urticaria.
Adverse reactions not reported in pediatric patients but are considered relevant to pediatric patients are photosensitivity reaction dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leucopenia, and blurred vision.
Adverse reactions identified during post approval use of pantoprazole were asthenia, fatigue, malaise, pancytopenia, agranulocytosis, anaphylaxis (including anaphylactic shock), clostridium difficile associated diarrhea, weight changes, hyponatremia, hypomagnesemia, severe dermatologic reactions (some fatal), including erythema multiforme, stevens-johnsons syndrome, and toxic epidermal necrolysis (TEN, some fatal), and angioedema (Quincke's edema), rhabdonmyolysis, bone fracture, ageusia dysgeusiaa interstitial nephritis, hepatocellular demage leading to jaundice and hepatic failure, hallucination and confusion, insomnia, and somnolence.

OVERDOSE
There are no known symptoms of overdose in man. Systemic exposure with up to 240mg administered intravenously over 2 minutes, were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor. In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Proton pump inhibitors.
Pantoprazole is a first-generation proton pump inhibitor (PPI). This drug acts to decrease gastric acid secretion, which reduces stomach acidity. Pantoprazole administration leads to long-lasting inhibition of gastric acid secretion. Hydrochloric acid (HCl) secretion into the gastric lumen is a process regulated mainly by the H(+)/K(+)-ATPase of the proton pump, expressed in high quantities by the parietal cells of the stomach. ATPase is an enzyme on the parietal cell membrane that facilitates hydrogen and potassium exchange through the cell, which normally results in the extrusion of potassium and formation of HCl (gastric acid).
Proton pump inhibitors such as pantoprazole are substituted benzimidazole derivatives, weak bases, which accumulate in the acidic space of the parietal cell before being converted in the canaliculi (small canal) of the gastric parietal cell, an acidic environment, to active sulfenamide derivatives. This active form then makes disulfide bonds with important cysteines on the gastric acid pump, inhibiting its function. Specifically, pantoprazole binds to the sulfhydryl group of H+, K+-ATPase, which is an enzyme implicated in accelerating the final step in the acid secretion pathway. The enzyme is inactivated, inhibiting gastric acid secretion. The inhibition of gastric acid secretion is stronger with proton pump inhibitors such as pantoprazole and lasts longer than with the H(2) antagonists.

PHARMACOKINETIC PROPERTIES
Absorption
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. The absolute bioavailability from the tablet was found to be about 77 %.
Distribution
Pantozole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.
Metabolism
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.
Excretion
Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole, the rest is excreted with the faeces.

INCOMPATIBILITY
None stated.

Storage and handling instructions
Store protected from light & moisture, at a temperature not exceeding 30°C.
Tablet should be swallowed whole and not chewed or crushed.
Keep all medicines out of reach of children.

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