PANTOPRAZOLE (Systemic)

Category

Gastric acid pump inhibitor ; antiulcer agent.

Indications

Note: Bracketed information in theIndications section refers to uses that are not included in U.S. product labeling.

Accepted

Gastroesophageal reflux disease [GERD] (treatment)¾Pantoprazole is indicated for the short-term (up to 8 weeks) treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD). 1, 9, 12

[Gastroesophageal reflux disease [GERD] (prophylaxis)]¾Pantoprazole is indicated for the prevention of relapse in patients with reflux esophagitis. 12

[Ulcer, duodenal (treatment)]¾Pantoprazole is indicated for short-term (up to 4 weeks) treatment for symptom relief and healing in patients with active duodenal ulcer. 1, 12

[Ulcer, duodenal, Helicobacter pylori-associated (treatment)]¾ Pantoprazole, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for treatment of patients with an active duodenal ulcer who are H. pyloripositive. 12

[Ulcer, gastric (treatment)]¾Pantoprazole is indicated for short-term (up to 8 weeks) treatment in patients with active benign gastric ulcer. 1, 12

Mechanism of action/Effect:

Pantoprazole is a proton pump inhibitor. It accumulates in the acidic compartment of parietal cells and is converted to the active form, a sulfenamide, which binds to hydrogen-potassium-ATP-ase at the secretory surface of gastric parietal cells. Inhibition of hydrogen-potassium-ATP-ase blocks the final step of gastric acid production, leading to inhibition of both basal and stimulated acid secretion. The duration of inhibition of acid secretion does not correlate with the much shorter elimination half-life of pantoprazole. 1, 6, 7

Other actions/effects:

Pantoprazole reduced in vitro counts of H pylori more than four times at pH 4 (no effect was obtained at pH 7). A minimum inhibitory concentration of 0.064 to 0.25 mg/mL (depending on H pylori strain) was determined for pantoprazole, with significant decreases obtained as low as 0.016 mg/mL. 8, 10

Onset of action:

Gastric acid suppression (pentagastrin-stimulated)¾51% on day 1. 1

Time to peak concentration:

Oral (enteric-coated)¾ 2 to 3 hours 1

Peak serum concentration:

Oral dose, 40 mg¾ 2.5 mg per liter 1

IV, 40 mg, 15-minute infusion, 4.62 microgram per mL 1

Time to peak effect:

Acid secretion decreased by 85% on day 7 after administration of oral pantoprazole 40 mg. 9

Duration of action:

Acid secretion returns to normal levels without rebound within 1 week. 9

Precautions to Consider

Carcinogenicity

A moderate increase in enterochromaffin-like (ECL) cell density was apparent after one year among 39 patients, the majority taking 40 to 80 mg pantoprazole for up to 5 years. ECL density appeared to plateau after 4 years. 9

ECL hyperplasia and ECL carcinoid were produced in male Sprague-Dawley (SD) rats at pantoprazole doses of ³50 mg per kg daily and ³0.5 mg per kg daily in female SD rats after 17 months, most likely due to elevated gastrin levels during chronic therapy. ECL-cell neoplasms did not occur over 24 months observations in mice receiving 5, 25, or 150 mg per kg daily. 1

Tumorigenicity

Pantoprazole doses ³50 mg per kg caused a slight increased frequency of hepatocellular tumor in rats, while in female mice dose of 150 mg per kg also resulted in an increased frequency. However, in both animals, the incidence of hepatocellular tumor was within historical control ranges for the strains tested. The tumors were characterized as late-appearing and primarily benign. Exposure to these unusually large doses for prolonged periods is associated with enzyme induction in rodents, leading to hepatomegaly and centrilobular hypertrophy. These findings not associated with the lower clinical doses and are apparently not applicable to human exposure. 1

An increased incidence of thyroid tumor in rats, although within the historical ranges for the strain tested, was observed following exposure to pantoprazole 200 mg per kg daily. Pantoprazole-induced liver enzyme induction results in increased metabolism of thyroid hormone, leading in turn to increased

production of TSH, with subsequent increased trophic changes within the thyroid gland. No similar effects have been observed in humans following exposure to usual clinical doses. 1

Pregnancy/Reproduction

Pregnancy¾Adequate and well-controlled studies in humans have not been done.
Animal studies have demonstrated that pantoprazole crosses the placental barrier; however, no teratogenic effects were observed. Doses of 15 mg per kg resulted in delayed fetal skeletal development. 1, 9, 10

FDA Pregnancy Category B.

Breast-feeding

It is not known whether pantoprazole is distributed into human breast milk. However, pantoprazole or its metabolites are distributed into the milk of rats (maximally 0.02% of an administered dose is excreted in the breast milk). Because pantoprazole has been shown to cause tumorigenic effects in animals, a decision should be made as to whether nursing should be discontinued or the medication withdrawn, taking into account the importance of pantoprazole to the mother. 1, 9, 10

Pediatrics

Appropriate studies on the relationship of age to the effects of pantoprazole have not been performed in the pediatric population. Safety and efficacy have not been established. 1, 9

Geriatrics

Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of pantoprazole in the elderly. Efficacy and safety are similar to those reported for younger adults. 1, 9

Pharmacogenetics

No differences in efficacy or safety between men and women are apparent.
Approximately 3% of Caucasians and African-Americans and between 17% and 23% of Asians have deficiency of the CYP2C19 hepatic enzyme system, resulting in slow metabolism. Although certain pharmacokinetic values such as half-life and serum concentrations of pantoprazole will be enhanced in these patients, no specific dose adjustments are recommended, and no differences in safety or efficacy are apparent. 9

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Pantoprazole, by increasing gastric pH, has the potential to affect the bioavailability of any medication for which absorption is pH-dependent. Also, pantoprazole may prevent the degradation of acid-labile drugs. 1

However, pantoprazole, although metabolized by hepatic cytochrome P 450 systems, does not appear to either inhibit or induce cytochrome P 450 enzyme activity. To date, no clinically significant interactions have been noted for such commonly used drugs as diazepam, phenytoin, nifedipine, theophylline, digoxin, warfarin, or oral contraceptives. 1

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Gastrin, serum 1

(a moderate increase in fasting serum gastrin during treatment 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Hepatic disease, chronic, current or history of

(may result in slight increase in serum concentrations and may increase exposure and decrease elimination of pantoprazole; should be used only cautiously in patients with mild-to-moderate hepatic impairment and should be avoided in patients with cirrhosis or more severe hepatic disease 1, 9)

Sensitivity to pantoprazole 1

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Blurred vision; depression ; eosinophilia (black, tarry stools; chest pain; chills ; cough; fever; painful or difficult urination; shortness of breath; sore throat; sores, ulcers, or white spots on lips or in mouth; swollen glands; unusual bleeding or bruising; unusual tiredness or weakness); exfoliative dermatitis (blisters on skin; chills; fever; general feeling of discomfort or illness; red, thickened, or scaly skin; swollen and/or painful glands; unusual bruising); hematuria (blood in urine; lower back pain; pain or burning while urinating); impotence (loss in sexual ability, desire, drive, or performance ;

decreased interest in sexual intercourse; inability to have or keep an erection); maculopapular rash (skin rash); paresthesia (burning, crawling, itching, numbness, prickling, "pins and needles" , or tingling feelings); photophobia (eye pain when looking at bright light; increased sensitivity of eyes to light) 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Diarrhea¾ (1.5%); headache¾(1.3%) ; malaise (general feeling of discomfort or illness; unusual tiredness or weakness) 1

Rare

Acne; alopecia (hair loss; thinning of hair); appetite, increased or decreased; asthenia (loss of strength or energy; muscle pain or weakness; unusual weak feeling)¾(0.3%); constipation; dizziness ¾(0.7%); dyspepsia (acid or sour stomach; belching ; heartburn; indigestion; stomach discomfort upset or pain); eructation, acid (belching; bloated full feeling ; excess air or gas in stomach); insomnia (sleeplessness; trouble sleeping; unable to sleep); nausea ; nervousness; pruritus (itching skin)¾(0.5%) ; somnolence (sleepiness or unusual drowsiness); tinnitus (continuing ringing or buzzing or other unexplained noise in ears; hearing loss); tremor; urticaria (hives or welts; itching; redness of skin; skin rash); vertigo (dizziness or light-headedness; feeling of constant movement of self or surroundings; sensation of spinning); xerostomia (dry mouth; thirst) 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Clinical effects of overdose

No adverse effects were reported in single-agent overdose with pantoprazole in doses of 400 and 600 mg. Death following multi-agent ingestion was attributed to chloroquine and zopiclone rather than pantoprazole. 9

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Limited human overdose data available with any proton pump inhibitors. Signs or symptoms of overdose may include: 11 mild tachycardia; vasodilation; somnolence; confusion; , headache; blurred vision; abdominal pain,; nausea & vomiting
Treatment of overdose

Decontamination¾ activated charcoal, gastric lavage. 11

Symptomatic and supportive¾ therapy as indicated. 1, 11

Monitoring parameters¾ Cardiac monitoring and blood pressure evaluation with significant overdose. Monitor fluid status and electrolytes with prolonged vomiting. 11

Due to extensive protein binding, pantoprazole is not readily dialyzable. 1

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Pantoprazole (Systemic).
In providing consultation, consider advising the patient on the following (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to pantoprazole
Pregnancy¾Causes delayed fetal skeletal development in animal studies
Breast-feeding¾Distributed into milk in animal studies; may cause potentially serious adverse effects in nursing infants
Use in children¾Safety and efficacy not established in children
Other medical problems, especially liver disease or history of
Proper use of this medication

Taking the tablet in the morning, with or without food

May take antacids for relief of pain, unless otherwise instructed by physician

Swallowing tablet form of this medication whole; not crushing, breaking, or chewing the tablet

>> Compliance with full course of therapy

>> Proper dosing
Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress

Side/adverse effects

Signs of potential side effects, especially blurred vision, depression, eosinophilia, exfoliative dermatitis, hematuria, impotence, maculopapular rash, paresthesia, and photophobia

General Dosing Information

In the treatment of gastroesophageal reflux disease and gastric ulcer, relief of symptoms usually occurs within 2 weeks and healing within 4 weeks. Therapy should not exceed 8 weeks. 1, 9, 12 Controlled studies of pantoprazole used as maintenance therapy to prevent reflux esophagitis recurrence have not been conducted beyond 12 months, although in a limited number of patients have received continuous

maintenance treatment for up to 8 years. 12 In the treatment of duodenal ulcer, relief of symptoms usually occurs within 1 week and healing within 2 weeks. Therapy should not exceed 4 weeks. 1, 9

Since pantoprazole is acid-labile , it is administered as an enteric-coated tablet to prevent gastric decomposition and to increase bioavailability. Tablets should be swallowed whole, and not split, chewed, or crushed. 1, 9, 12

Diet/Nutrition

Tablets may be taken before, during, or following the morning meal. 12 Neither food nor antacids altered the bioavailability of pantoprazole. 1

Oral Dosage Forms

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

PANTOPRAZOLE TABLETS

Usual adult dose

Gastroesophageal reflux disease (treatment) ¾
Oral, 40 milligrams (mg) per day for up to four to eight weeks. An additional four to eight-week course may be considered in patients who have not healed after four to eight weeks of treatment. 1, 9, 12

[Gastroesophageal reflux disease (prophylaxis)]¾
Oral, 20 mg once a day in the morning. Dose can be increased to 40 mg once a day in the morning in the case of recurrence. 12

[Ulcer, duodenal, H. pylori-associated (treatment)]¾
Oral, triple therapy regimens of pantoprazole 40 mg, plus clarithromycin 500 mg, plus either amoxicillin 1000 mg or metronidazole 500 mg, in which all three medications are taken two times a day for seven days. 12

[Ulcer, duodenal (treatment)]¾
Oral, 40 mgper day for up to two weeks. An additional two-week course may be considered in patients who have not healed after two weeks of treatment. 1, 12

[Ulcer, gastric (treatment)]¾
Oral, 40 mg per day for up to four weeks. An additional four-week course may be considered in patients who have not healed after four weeks of treatment. 1, 12

Usual pediatric dose

Safety and efficacy have not been established. 1

Usual geriatric dose

See Usual adult dose.

Strength(s) usually available
U.S.¾40 mg pantoprazole [equivalent to 45.1 mg pantoprazole sodium sesquihydrate] (Rx)[Protonix]

Canada¾20 mg pantoprazole [equivalent to 22.6 mg pantoprazole sodium sesquihydrate] (Rx)[Pantoloc]

40 mg pantoprazole [equivalent to 45.1 mg pantoprazole sodium sesquihydrate] (Rx)[Pantoloc]

Packaging and storage:

Store at 15 to 30° C (59 and 86° F). 1, 9

Auxiliary labeling:

· Do not chew or crush tablets.
· Swallow tablets whole with a full glass (8 ounces) of water.
· Take with food or antacids.

References

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6 Simon B, Mueller P, Hartmann M et al: Pentagrastin-stimulated gastric acid secretion and pharmacokinetics following single and repeated intravenous administration of the gastic H+, K+ -ATPase-inhibitor pantoprazole (BY1023/SK&F96022) in healthy volunteers. Z Gastroenterol 1990; 28:443-447.

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8 Suerbaum S, Leying H, Klemm K et al: Antibacterial activity of pantoprazole and omeprazole against Heliobacter pylori. Eur J Clin Microbiol Infect Dis 1991; 10:92-93.

9 Product Information: Protonix(R), pantoprazole sodium. Wyeth-Ayerst, Philadelphia, PA (PI revised 2/2000) reviewed 2/2000.

10 Fachinformation: Pantozol(R), pantoprazole. Byk-Gulden, Konstanz, 1995.

11 Editorial Staff: Omeprazole and Related Agents (Management/Treatment Protocol). In: Toll LL & Hurlbut KM (Eds): POISINDEX(R) System. MICROMEDEX, Inc., Englewood, Colorado (Edition 105 Expires 05/2000).

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