



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PANTOPRAZOLE SODIUM FOR DELAYED-RELEASE ORAL SUSPENSION safely and effectively. See full prescribing information for PANTOPRAZOLE SODIUM FOR DELAYED-RELEASE ORAL SUSPENSION.

PANTOPRAZOLE SODIUM for delayed-release oral suspension

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Warnings and Precautions, Fundic Gland Polyps (5.9) 06/2018

INDICATIONS AND USAGE

Pantoprazole sodium is a proton pump inhibitor (PPI) indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD) (1.1)
- Maintenance of Healing of Erosive Esophagitis (1.2)
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (1.3)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Short-Term Treatment of Erosive Esophagitis Associated With GERD (2.1)	40 mg	Once Daily for up to 8 wks
Children (5 years and older) \geq 40 kg	40 mg	Once Daily for up to 8 wks

Maintenance of Healing of Erosive Esophagitis (2.1)

Adults	40 mg	Once Daily*
--------	-------	-------------

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (2.1)

Adults	40 mg	Twice Daily
--------	-------	-------------

* Controlled studies did not extend beyond 12 months

See full prescribing information for administration instructions

DOSAGE FORMS AND STRENGTHS

- For Delayed-Release Oral Suspension: 40 mg pantoprazole (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (4)
- Patients receiving rilpivirine-containing products (4.7)

Revised: 02/2020

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE

- Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
 - Maintenance of Healing of Erosive Esophagitis
 - Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome

2 DOSAGE AND ADMINISTRATION

- Recommended Dosing Schedule
- Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Presence of Gastric Malignancy
- Acute Interstitial Nephritis
- Clostridium difficile*-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B-12) Deficiency
- Hypomagnesemia
- Tumorigenicity
- Fundic Gland Polyps
- Interference with Investigations for Neuroendocrine Tumors
- Interference with Urine Screen for THC
- Concomitant Use of Pantoprazole with Methotrexate

6 ADVERSE REACTIONS

- Clinical Trials Experience

WARNINGS AND PRECAUTIONS

- Gastric Malignancy:** In adults, symptomatic response does not preclude presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
- Acute Interstitial Nephritis:** Observed in patients taking PPIs. (5.2)
- Clostridium difficile*-Associated Diarrhea:** PPI therapy may be associated with increased risk of *Clostridium difficile*-associated diarrhea. (5.3)
- Bone Fracture:** Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus:** Mostly cutaneous; new onset or exacerbation of existing disease; discontinue pantoprazole and refer to specialist for evaluation. (5.5)
- Cyanocobalamin (Vitamin B-12) Deficiency:** Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.6)
- Hypomagnesemia:** Reported rarely with prolonged treatment with PPIs. (5.7)
- Fundic Gland Polyps:** Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.9)

ADVERSE REACTIONS

Most common adverse reactions are:

- For adult use (>2%): headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. (6.1)
- For pediatric use (>4%): URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for a list of clinically important drug interactions (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2020

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole. (See Drug Interactions (7)).

8.2 Lactation

Pantoprazole sodium is a proton pump inhibitor (PPI) indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD) (1.1)
- Maintenance of Healing of Erosive Esophagitis (1.2)
- Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome (1.3)

DOSAGE AND ADMINISTRATION

Pantoprazole sodium is a proton pump inhibitor (PPI) indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD) (1.1)
- Maintenance of Healing of Erosive Esophagitis (1.2)
- Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome (1.3)

DOSAGE FORMS AND STRENGTHS

- For Delayed-Release Oral Suspension: 40 mg pantoprazole (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (4)
- Patients receiving rilpivirine-containing products (4.7)

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE

- Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
 - Maintenance of Healing of Erosive Esophagitis
 - Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome

2 DOSAGE AND ADMINISTRATION

- Recommended Dosing Schedule
- Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Presence of Gastric Malignancy
- Acute Interstitial Nephritis
- Clostridium difficile*-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B-12) Deficiency
- Hypomagnesemia
- Tumorigenicity
- Fundic Gland Polyps
- Interference with Investigations for Neuroendocrine Tumors
- Interference with Urine Screen for THC
- Concomitant Use of Pantoprazole with Methotrexate

6 ADVERSE REACTIONS

- Clinical Trials Experience

WARNINGS AND PRECAUTIONS

- Gastric Malignancy:** In adults, symptomatic response does not preclude presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
- Acute Interstitial Nephritis:** Observed in patients taking PPIs. (5.2)
- Clostridium difficile*-Associated Diarrhea:** PPI therapy may be associated with increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. (See Adverse Reactions (6.2)). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- Bone Fracture:** Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus:** Mostly cutaneous; new onset or exacerbation of existing disease; discontinue pantoprazole and refer to specialist for evaluation. (5.5)
- Cyanocobalamin (Vitamin B-12) Deficiency:** Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.6)
- Hypomagnesemia:** Reported rarely with prolonged treatment with PPIs. (5.7)
- Fundic Gland Polyps:** Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.9)

ADVERSE REACTIONS

Most common adverse reactions are:

- For adult use (>2%): headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. (6.1)
- For pediatric use (>4%): URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for a list of clinically important drug interactions (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2020

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

See full prescribing information for a list of clinically important drug interactions (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2020

5.7 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. (See Adverse Reactions (5.7)).

5.8 Tumorigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown. (See Nonclinical Toxicology (13.1)).

5.9 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

5.10 Interference with Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop pantoprazole sodium for delayed-release oral suspension treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary. (See Clinical Pharmacology (12.2)).

5.11 Interference with Urine Screen for THC

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole. (See Drug Interactions (7)).

5.12 Concomitant Use of Pantoprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients. (See Drug Interactions (7)).

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Interstitial Nephritis. (See Warnings and Precautions (5.2))
- Clostridium difficile*-Associated Diarrhea. (See Warnings and Precautions (5.3))
- Bone Fracture. (See Warnings and Precautions (5.4))
- Cutaneous and Systemic Lupus Erythematosus. (See Warnings and Precautions (5.5))
- Cyanocobalamin (Vitamin B-12) Deficiency. (See Warnings and Precautions (5.6))
- Hypomagnesemia. (See Warnings and Precautions (5.7))
- Fundic Gland Polyps. (See Warnings and Precautions (5.9))

6.1 Clinical Trials Experience

The adverse reaction profiles for pantoprazole sodium for delayed-release oral suspension and pantoprazole sodium delayed-release tablets are similar. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral pantoprazole (20 mg or 40 mg), 292 patients on an H₂ receptor antagonist, 46 patients on another PPI, and 89 patients on placebo. The most frequently occurring adverse reactions are listed in Table 3.

Table 3: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of \geq 2%

	Pantoprazole (n=1,473)	Comparators (n=345)	Placebo (n=82)
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7.0	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3.0	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for pantoprazole in clinical trials with a frequency of \leq 2% are listed below by body system:

Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial edema

Gastrointestinal: constipation, dry mouth, hepatitis

Hematologic: leukopenia, thrombocytopenia

Metabolic/Nutritional: elevated CK (creatinine kinase), generalized edema, elevated triglycerides, liver enzymes elevated

Musculoskeletal: myalgia

Nervous: depression, vertigo

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Pediatric Patients:

Safety of pantoprazole in the treatment of EE associated with GERD was evaluated in pediatric patients ages 1 year through 16 years in three clinical trials. Safety trials involved pediatric patients with EE; however, as EE is uncommon in the pediatric population, 249 pediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. All adult adverse reactions to pantoprazole are considered relevant to pediatric patients. In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions include: URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.

For safety information in patients less than 1 year of age see Use in Specific Populations (8.4).

Additional adverse reactions that were reported for pantoprazole in pediatric patients in clinical trials with a frequency of \leq 4% are listed below by body system:

Body as a Whole: allergic reaction, facial edema

Gastrointestinal: constipation, flatulence, nausea

Metabolic/Nutritional: elevated triglycerides, elevated liver enzymes, elevated CK (creatinine kinase)

Musculoskeletal: arthralgia, myalgia

Nervous: dizziness, vertigo

Skin and Appendages: urticaria

The following adverse reactions seen in adults in clinical trials were not reported in pediatric patients in clinical trials, but are considered relevant to pediatric patients: photosensitivity reaction, dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leukopenia, and blurred vision.

Zollinger-Ellison (ZE) Syndrome

In clinical studies of ZE Syndrome, adverse reactions reported in 35 patients taking pantoprazole 80 mg/day to 240 mg/day for up to 2 years were similar to those reported in adult patients with GERD.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of pantoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are listed below by body system:

Gastrointestinal Disorders: fundic gland polyps

General Disorders and Administration Conditions: asthenia, fatigue, malaise

Hematologic: pancytopenia, agranulocytosis

Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure

Immune System Disorders: anaphylaxis (including anaphylactic shock), systemic lupus erythematosus

Infections and Infestations: *Clostridium difficile* associated diarrhea

Investigations: weight changes

Metabolism and Nutritional Disorders: hyponatremia, hypomagnesemia

Musculoskeletal Disorders: rhabdomyolysis, bone fracture

Nervous: agnosia, dysgeusia

Psychiatric Disorders: hallucination, confusion, insomnia, somnolence

Renal and Urinary Disorders: interstitial nephritis

Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal), angioedema (Quincke's edema) and cutaneous lupus erythematosus

7 DRUG INTERACTIONS

Table 4 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with pantoprazole and instructions for preventing or managing them. Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table 4: Clinically Relevant Interactions Affecting Drugs Coadministered with Pantoprazole and Interactions with Diagnostics

Antiretrovirals

Clinical Impact: The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

- Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with pantoprazole may reduce antiviral effect and promote the development of drug resistance.
- Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity of the antiretroviral drugs.
- There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.

Intervention: Rilpivirine-containing products: Concomitant use with pantoprazole is contraindicated. (See Contraindications (4)). See prescribing information. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with pantoprazole. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.

Warfarin

Clinical Impact: Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Intervention: Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.

Clopidogrel

Clinical Impact: Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. (See Clinical Pharmacology (12.3)).

Intervention: No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole sodium for delayed-release oral suspension.

Methotrexate

Clinical Impact: Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite, hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted. (See Warnings and Precautions (5.12)).

Intervention: A temporary withdrawal of pantoprazole may be considered in some patients receiving high-dose methotrexate.

Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)

Clinical Impact: Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

Intervention: Mycophenolate mofetil (MMF): Coadministration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. (See Clinical Pharmacology (12.3)). The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving pantoprazole and MMF. Use pantoprazole with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.

Pantoprazole sodium for delayed-release oral suspension is supplied as a for delayed-release oral suspension in unit-dose packets available in one strength 40 mg pantoprazole, (equivalent to 45.1 mg of pantoprazole sodium), contains the following inactive ingredients: calcium stearate, croscopolone, ferric oxide yellow, hydroxypropyl cellulose, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polyorbital 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, and triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pantoprazole is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H⁺, K⁺)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

12.2 Pharmacodynamics

Pantoprazole sodium for delayed-release oral suspension, 40 mg has been shown to be comparable to pantoprazole sodium delayed-release tablets in suppressing pantoprazole-stimulated MAO in patients (n = 49) with GERD and a history of EE. In this multicenter, pharmacodynamic crossover study, a 40 mg oral dose of pantoprazole sodium for delayed-release oral suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of pantoprazole sodium delayed-release tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pantoprazole-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20 mg to 80 mg) or a single dose of intravenous (20 mg to 120 mg) pantoprazole in healthy subjects. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies, pantoprazole, at all doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was <3 and <4. Treatment with 40 mg of pantoprazole produced significantly greater increases in gastric pH than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown in Table 5.

Table 5: Effect of Single Daily Doses of Oral Pantoprazole on Intraesophageal pH

Time	Median pH on day 7			
	Placebo	20 mg	40 mg	80 mg
8 a.m. to 8 a.m. (24 hours)	1.3	2.9*	3.8*	3.9*
8 a.m. to 10 p.m. (Daytime)	1.6	3.2*	4.4*	4.8*
10 p.m. to 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

*Significantly different from placebo

**Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of EE in which 68 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with pantoprazole sodium delayed-release tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from baseline in treatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following short-term treatment with pantoprazole, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by PPIs. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery [see *Nonclinical Toxicology* (13.1)].

Endocrine Effects

In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T₃), thyroxine (T₄), thyroid-stimulating hormone (TSH), thyroxine-binding protein, thyroxine, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1-year study of GERD patients treated with pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels of T₃, T₄, and TSH.

12.3 Pharmacokinetics

Pantoprazole sodium delayed-release tablets are prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaffected with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

In extensive metabolizers with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.5 mcg/mL, the time to reach the peak concentration (t_{max}) is 2.5 h, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 mcg•h/mL (range 1.4 to 13.3 mcg•h/mL). Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6 to 14.0 L/h, and its apparent volume of distribution is 11.0 to 23.6 L.

A single oral dose of pantoprazole sodium for delayed-release oral suspension, 40 mg, was shown to be bioequivalent when administered to healthy subjects (N = 22) as granules sprinkled over a teaspoonful of applesauce, as granules mixed with apple juice, or mixed with apple juice followed by administration through a nasogastric tube. The plasma pharmacokinetic parameters from a crossover study in healthy subjects are summarized in Table 6.

Table 6: Pharmacokinetics Parameters (mean ± SD) of Pantoprazole Sodium for Delayed-Release Oral Suspension at 40 mg

Pharmacokinetic Parameters	Granules in Applesauce	Granules in Apple Juice	Granules in Nasogastric Tube
AUC (mcg•h/mL)	4.0 ± 1.5	4.0 ± 1.5	4.1 ± 1.7
C _{max} (mcg/mL)	2.0 ± 0.7	1.9 ± 0.5	2.2 ± 0.7
t _{max} (hr) ^a	2.0	2.5	2.0

^aMedian values are reported for t_{max}.

Absorption

After administration of a single or multiple oral 40 mg doses of pantoprazole sodium delayed-release tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C_{max} was 2.5 mcg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

Administration of pantoprazole sodium delayed-release tablets with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole sodium delayed-release tablets may be taken without regard to timing of meals.

Administration of pantoprazole granules, 40 mg, with a high-fat meal delayed median time to peak plasma concentration by 2 hours. With a concomitant high-fat meal, the C_{max} and AUC of pantoprazole granules, 40 mg, sprinkled on applesauce decreased by 51% and 29%, respectively. Thus, pantoprazole sodium for delayed-release oral suspension should be taken approximately 30 minutes before a meal.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Elimination

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Excretion

After a single oral or intravenous dose of ¹⁴C-labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was

no renal excretion of unchanged pantoprazole.

Specific Populations

Geriatric Patients

Only slight to moderate increases in the AUC (43%) and C_{max} (26%) of pantoprazole were found in elderly subjects (64 to 76 years of age) after repeated oral administration, compared with younger subjects [see *Use in Specific Populations* (8.5)].

Pediatric Patients

The pharmacokinetics of pantoprazole were studied in children less than 16 years of age in four randomized, open-label clinical trials in pediatric patients with presumed/proven GERD. A pediatric granule formulation was studied in children through 5 years of age, and pantoprazole sodium delayed-release tablets were studied in children older than 5 years.

In a population PK analysis, total clearance increased with increasing bodyweight in a non-linear fashion. The total clearance also increased with increasing age only in children under 3 years of age.

Neonate through 5 Years of Age [See *Use in Specific Populations* (8.4)]

Children and Adolescents 6 through 16 Years of Age

The pharmacokinetics of pantoprazole sodium delayed-release tablets were evaluated in children ages 6 through 16 years with a clinical diagnosis of GERD. The PK parameters following a single oral dose of 20 mg or 40 mg of pantoprazole sodium delayed-release tablets in children ages 6 through 16 years were highly variable (%CV ranges 40 to 80%). The geometric mean AUC estimated from population PK analysis after a 40 mg pantoprazole sodium delayed-release tablets in pediatric patients was about 39% and 10% higher respectively in 6 to 11 and 12 to 16 year-old children, compared to that of adults (Table 7).

Table 7: PK Parameters in Children and Adolescents 6 through 16 years with GERD receiving 40 mg Pantoprazole Sodium Delayed-Release Tablets

	6 to 11 years (n=12)	12 to 16 years (n=11)
C _{max} (mcg/mL) ^a	1.8	1.8
t _{max} (hr) ^b	2.0	2.0
AUC (mcg•h/mL) ^a	6.9	5.5
CL/F (L/h) ^b	6.6	6.8

^aGeometric mean values

^bMedian values

Male and Female Patients

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men.

In pediatric patients ages 1 through 16 years there were no clinically relevant effects of gender on clearance of pantoprazole, as shown by population pharmacokinetic analysis.

Patients with Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.

Patients with Hepatic Impairment

In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7 to 9 hours and AUC values increased by 5- to 7-fold in hepatically-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatically-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.

Drug Interaction Studies

Effect of Other Drugs on Pantoprazole

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer] and clobidogrel), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates), and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered.

Effect of Pantoprazole on Other Drugs

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. In a crossover clinical study, 66 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. On Day 5, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (geometric mean ratio was 86%, with 90% CI to 93%) when pantoprazole was coadministered with clopidogrel as compared to clopidogrel administered alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 μM ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

Mycophenolate Mofetil (MMF)

Administration of pantoprazole 40 mg twice daily for 4 days and a single 1,000 mg dose of MMF approximately one hour after the last dose of pantoprazole to 12 healthy subjects in a cross-over study resulted in a 57% reduction in the C_{max} and 27% reduction in the AUC of MPA. Transplant patients receiving approximately 2,000 mg per day of MMF (n=12) were compared to transplant patients receiving approximately the same dose of MMF and pantoprazole 40 mg per day (n=21). There was a 78% reduction in the C_{max} and a 45% reduction in the AUC of MPA in patients receiving both pantoprazole and MMF [see *Drug Interactions* (7)].

Other Drugs

In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of the following drugs (cispripide, theophylline, diazepam [and its active metabolite, desmethyl-diazepam], phenytoin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, diclofenac, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl estradiol]). In other *in vivo* studies, dioxin, ethanol, glyburide, amiprynyne, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once-daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Antacids

There was also no interaction with concomitantly administered antacids.

12.5 Pharmacogenomics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations of (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 5.5 to 10 hours in adults, they still have minimal accumulation (23% or less) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.

Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

For non-pediatric poor metabolizers, a dose reduction should be considered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with pantoprazole doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50 kg person dosed with 40 mg/day. In the gastric fundus, treatment with 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment with 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day of pantoprazole, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment with 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day of pantoprazole, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment with 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment with 5 to 150 mg/kg/day also produced gastric-fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not possible.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* A52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450

mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

14 CLINICAL STUDIES

Pantoprazole sodium delayed-release tablets were used in the following clinical trials.

14.1 Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

Adult Patients

A US multicenter, double-blind, placebo-controlled study of pantoprazole sodium delayed-release tablets 10 mg, 20 mg, or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3, and 10% had grade 4. The percentages of patients healed (per protocol, n = 541) in this study are shown in Table 8.

Table 8: Erosive Esophagitis Healing Rates (Per Protocol)

Week	Pantoprazole Sodium Delayed-Release Tablets				Placebo (n = 68)
	10 mg daily (n = 153)	20 mg daily (n = 158)	40 mg daily (n = 162)		
4	45.6%*	58.4%*	75.0%*	14.3%	
8	66.0%*	83.5%*	92.6%*	39.7%	

* (p < 0.001) pantoprazole sodium delayed-release tablets versus placebo

** (p < 0.05) versus 10 mg or 20 mg pantoprazole sodium delayed-release tablets

† (p < 0.05) versus 10 mg pantoprazole sodium delayed-release tablets

In this study, all pantoprazole sodium delayed-release tablets treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 40 mg and 20 mg pantoprazole sodium delayed-release tablets treatment groups. The 40 mg dose of pantoprazole sodium delayed-release tablets resulted in healing rates significantly greater than those found with either the 20 mg or 10 mg dose.

A significantly greater proportion of patients taking pantoprazole sodium delayed-release tablets 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation, starting from the first night of treatment, compared with placebo. Patients taking pantoprazole sodium delayed-release tablets consumed significantly fewer antacid tablets per day than those taking placebo.

Pantoprazole sodium delayed-release tablets 40 mg and 20 mg once daily were also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n = 212) are shown in Table 9.

Table 9: Erosive Esophagitis Healing Rates (Per Protocol)

Week	Pantoprazole Sodium Delayed-Release Tablets		Nizatidine (n = 70)
	20 mg daily (n = 72)	40 mg daily (n = 70)	
4	61.4%*	64.0%*	22.2%
8	79.2%*	82.9%*	41.4%

* (p < 0.001) pantoprazole sodium delayed-release tablets versus nizatidine

Once-daily treatment with pantoprazole sodium delayed-release tablets 40 mg or 20 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice-daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the pantoprazole sodium delayed-release tablets treatment groups experienced complete relief of nighttime heartburn and regurgitation, starting on the first day and of daytime heartburn on the second day, compared with those taking nizatidine 150 mg twice daily. Patients taking pantoprazole sodium delayed-release tablets consumed significantly fewer antacid tablets per day than those taking nizatidine.

Pediatric Patients Ages 5 Years through 16 Years

The efficacy of pantoprazole sodium delayed-release tablets in the treatment of EE associated with GERD in pediatric patients ages 5 years through 16 years was extrapolated from adequate and well-conducted trials in adults, as the pathophysiology is thought to be the same. Four pediatric patients with endoscopically diagnosed EE were studied in multicenter, randomized, double-blind, parallel-treatment trials. Children with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥ 2) were treated once daily for 8 weeks with one of two dose levels of pantoprazole sodium delayed-release tablets (20 mg or 40 mg). All 4 patients with EE were healed (Hetzel-Dent score of 0 or 1) at 8 weeks.

14.2 Long-Term Maintenance of Healing of Erosive Esophagitis

Two independent, multicenter, randomized, double-blind, comparator-controlled trials of identical design were conducted in adult GERD patients with endoscopically confirmed healed EE to demonstrate efficacy of pantoprazole sodium delayed-release tablets in long-term maintenance of healing. The two US studies enrolled 386 and 404 patients, respectively, to receive either 10 mg, 20 mg, or 40 mg of pantoprazole sodium delayed-release tablets once daily or 150 mg of ranitidine twice daily. As demonstrated in Table 10, pantoprazole sodium delayed-release tablets 40 mg and 20 mg were significantly superior to ranitidine at every timepoint with respect to the maintenance of healing. In addition, pantoprazole sodium delayed-release tablet 40 mg was superior to all other treatments studied.

Table 10: Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD) Maintenance: Percentage of Patients Who Remained Healed

	Pantoprazole Sodium Delayed-Release Tablets 20 mg daily	Pantoprazole Sodium Delayed-Release Tablets 40 mg daily	Ranitidine 150 mg twice daily
Study 1	n = 75	n = 74	n = 75
Month 1	91*	99*	68
Month 3	82*	93*	54
Month 6	76*	90*	44
Month 12	70*	86*	35
Study 2	n = 74	n = 68	n = 84
Month 1	89*	92*	62
Month 3	78*	91*	47
Month 6	72*	88*	39
Month 12	72*	83*	37

* (p < 0.05 vs. ranitidine)

† (p < 0.05 vs. pantoprazole sodium delayed-release tablets 20 mg)

Note: Pantoprazole sodium delayed-release tablets 40 mg was superior (p < 0.05) to ranitidine in Study 2, but not Study 1.

Pantoprazole sodium delayed-release tablet 40 mg was superior to ranitidine in reducing the number of daytime and nighttime heartburn episodes from the first through the twelfth month of treatment. Pantoprazole sodium delayed-release tablets 20 mg administered once daily, was also effective in reducing episodes of daytime and nighttime heartburn in one trial, as presented in Table 11.

Table 11: Number of Episodes of Heartburn (mean ± SD)

	Pantoprazole Sodium Delayed-Release Tablets 40 mg daily	Ranitidine 150 mg twice daily	
Month 1	Daytime	5.1 ± 1.6*	18.3 ± 1.6
	Nighttime	3.9 ± 1.1*	11.9 ± 1.1
Month 12	Daytime	2.9 ± 1.5*	17.5 ± 1.5
	Nighttime	2.5 ± 1.2*	13.8 ± 1.3

* (p < 0.001 vs. ranitidine, combined data from the two US studies)

14.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison Syndrome, with or without multiple endocrine neoplasia-type 1, pantoprazole sodium delayed-release tablets successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10 mEq/h in patients without prior acid-redu