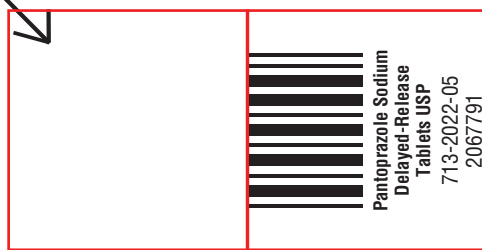


2D Data Matrix to be printed with
serial number on each leaflet.
The number should not be repeated

Note: Position of the pharma code and product name will
change as per the folding machine feasibility



HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PANTOPRAZOLE SODIUM delayed-release tablets, for oral use
Initial U.S. approval: 2000

RECENT MAJOR CHANGES

Warnings and Precautions, Severe Cutaneous Adverse Reactions (5.5) 03/2022
Hypomagnesemia and Mineral Metabolism (5.8) 03/2022

INDICATIONS AND USAGE

Pantoprazole sodium delayed-release tablet 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)

DOSE AND ADMINISTRATION

Indication	Dose	Frequency
Short-Term Treatment of Erosive Esophagitis Associated With GERD (2.1)		
Adults	40 mg	Once Daily for up to 8 wks
Children (5 years and older)		
≥ 15 kg to < 40 kg	20 mg	Once Daily for up to 8 wks
≥ 40 kg	40 mg	Once Daily
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

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosing Schedule
2.2 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Presence of Gastric Malignancy
5.2 Acute Tubulointerstitial Nephritis
5.3 *Clostridium difficile*-Associated Diarrhea
5.4 Bone Fracture
5.5 Severe Cutaneous Adverse Reactions
5.6 Cutaneous and Systemic Lupus Erythematosus
5.7 Cyanocobalamin (Vitamin B-12) Deficiency
5.8 Hypomagnesemia and Mineral Metabolism
5.9 Tumorigenicity
5.10 Fundic Gland Polyps
5.11 Interference with Investigations for Neuroendocrine Tumors
5.12 Interference with Urine Screen for THC
5.13 Concomitant Use of Pantoprazole Sodium with Methotrexate

6 ADVERSE REACTIONS

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Pantoprazole Sodium Delayed-Release Tablets are indicated for:

1.1 Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

Pantoprazole Sodium Delayed-Release Tablet is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE). For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of pantoprazole sodium delayed-release tablets may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.

1.2 Maintenance of Healing of Erosive Esophagitis

Pantoprazole Sodium Delayed-Release Tablets are indicated for maintenance of healing of EE and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

1.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Pantoprazole Sodium Delayed-Release Tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison (ZE) Syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing Schedule

Pantoprazole sodium is supplied as delayed-release tablets. The recommended dosages are outlined in Table 1.

Table 1. Recommended Dosing Schedule for Pantoprazole Sodium Delayed-Release Tablets

Indication	Dose	Frequency
Short-Term Treatment of Erosive Esophagitis Associated With GERD		
Adults	40 mg	Once daily for up to 8 weeks*
Children (5 years and older)		
≥ 15 kg to < 40 kg	20 mg	Once daily for up to 8 weeks
≥ 40 kg	40 mg	Once daily**
Maintenance of Healing of Erosive Esophagitis		
Adults	40 mg	Once daily**
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome		
Adults	40 mg	Twice daily**

* For adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of pantoprazole sodium delayed-release tablets may be considered.
** Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.
*** Controlled studies did not extend beyond 12 months

2.2 Administration Instructions

Directions for method of administration for each dosage form are presented in Table 2.

Table 2. Administration Instructions

Formulation	Route	Instructions*
Delayed-Release Tablets	Oral	Swallowed whole, with or without food

* Do not split, chew, or crush Pantoprazole Sodium Delayed-Release Tablets.
Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular scheduled time. Do not take 2 doses at the same time.

Pantoprazole Sodium Delayed-Release Tablets

Swallow Pantoprazole Sodium Delayed-Release Tablets whole, with or without food in the stomach. For patients unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of Pantoprazole Sodium Delayed-Release Tablets.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg, yellow to pale yellow, oval, biconvex, delayed-release tablets imprinted "H125" on one side with black ink and plain on the other side.
40 mg, yellow to pale yellow, oval, biconvex, delayed-release tablets imprinted "H126" on one side with black ink and plain on the other side.

4 CONTRAINDICATIONS

- Pantoprazole sodium delayed-release tablets are contraindicated in patients with known hypersensitivity to any component of the formulation or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis, and urticaria [see Warnings and Precautions (5.2), Adverse Reactions (6)].
• Proton pump inhibitors (PPIs), including pantoprazole sodium delayed-release tablets, are contraindicated in patients receiving rilpivirine-containing products [see Drug Interactions (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with pantoprazole sodium does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

5.2 Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue pantoprazole sodium delayed-release tablets and evaluate patients with suspected acute TIN [see Contraindications (4)].

5.3 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that PPI therapy like pantoprazole sodium may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions (6.2)]. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.4 Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Dosage and Administration (2), Adverse Reactions (6.2)].

5.5 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs [see Adverse Reactions (6.2)]. Discontinue pantoprazole sodium at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

5.6 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SACLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving pantoprazole sodium, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improved with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

5.7 Cyanocobalamin (Vitamin B-12) Deficiency

Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.8 Hypomagnesemia and Mineral Metabolism

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. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients. 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 (6.2)].

Consider monitoring magnesium and calcium levels prior to initiation of pantoprazole sodium and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

DOSE FORMS AND STRENGTHS

- Delayed-Release Tablets: 20 mg and 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)

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 Tubulointerstitial Nephritis:** Discontinue treatment and evaluate patients. (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)
• **Severe Cutaneous Adverse Reactions:** Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
• **Cutaneous and Systemic Lupus Erythematosus:** Mostly cutaneous; new onset or exacerbation of existing disease; discontinue pantoprazole sodium delayed-release tablet and refer to specialist for evaluation. (5.6)
• **Cyanocobalamin (Vitamin B-12) Deficiency:** Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.7)
• **Hypomagnesemia and Mineral Metabolism:** Reported rarely with prolonged treatment with PPIs. (5.8)
• **Fundic Gland Polyps:** Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.10)

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 Hetero Labs Limited at 1-866-495-1995 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: 05/2022

6.1 Clinical Trials Experience

- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

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8.2 Lactation
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14.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

5.9 Tumorigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole sodium. 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)].

5.10 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.

5.11 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 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)].

5.12 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 sodium [see Drug Interactions (7)].

5.13 Concomitant Use of Pantoprazole Sodium 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 Tubulointerstitial 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)]
- Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5.5)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.6)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.7)]
- Hypomagnesemia and Mineral Metabolism [see Warnings and Precautions (5.8)]
- Fundic Gland Polyps [see Warnings and Precautions (5.10)]

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 sodium (20 mg or 40 mg), 299 patients on an H₂-receptor antagonist, 46 patients on another PPI, and 82 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 >2%

	Pantoprazole sodium (n=1473) %	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 sodium in clinical trials with a frequency of ≤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 sodium 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 sodium 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 sodium in pediatric patients in clinical trials with a frequency of ≥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 sodium 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 sodium. 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: hypomagnesemia, hypocalcemia, hypokalemia, hyponatremia

Musculoskeletal Disorders: rhabdomyolysis, bone fracture

Nervous: agueusia, dysgeusia

Psychiatric Disorders: hallucination, confusion, insomnia, somnolence

Renal and Urinary Disorders: acute tubulointerstitial nephritis

Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, SJS/TEN, DRESS, AGEP, angioedema (Quincke's edema) and cutaneous lupus erythematosus

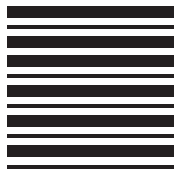
7 DRUG INTERACTIONS

Table 4 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with pantoprazole sodium 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 Co-Administered with Pantoprazole Sodium 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. <ul style="list-style-type: none">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 may increase toxicity of the antiretroviral drug.There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.

Antiretrovirals	
Intervention:	Ril



age group, the use of pantoprazole sodium for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Animal Toxicity Data

In a pre- and post-natal development study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure(AUC) in children aged 6 to 11 years at a dose of 40 mg) on postnatal day (PND 4) through PND 21, in addition to lactational exposure through milk. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in children aged 6 to 11 years at the 40 mg dose) and higher doses. Changes in bone parameters were partially reversible following a recovery period. In neonatal/juvenile animals (rats and dogs) toxicities were similar to those observed in adult animals, including gastric alterations, decreases in red cell counts, increases in lipids, enzyme induction and hepatocellular hypertrophy. An increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, was observed in the fundic mucosa of stomachs in repeated-dose studies. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

8.5 Geriatric Use

In short-term US clinical trials, EE healing rates in the 107 elderly patients (≥65 years old) treated with pantoprazole sodium were similar to those found in patients under the age of 65. The incidence rates of adverse reactions and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

10 OVERDOSAGE

Experiences in patients taking very high doses of pantoprazole sodium (greater than 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of pantoprazole sodium.

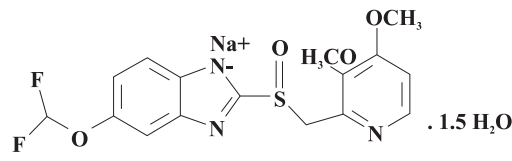
Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypocoagivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

If overexposure to pantoprazole sodium occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdose.

11 DESCRIPTION

The active ingredient in Pantoprazole Sodium Delayed-Release Tablets, USP, a PPI, is a substituted benzimidazole, 5-(Difluoromethyl)-2-[(1,3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl)benzimidazole sodium salt, sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{18}H_{14}F_2N_4NaO_5S$. 1.5 H_2O , with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate, USP is a white to off-white powder. Pantoprazole sodium sesquihydrate, USP is freely soluble in water, in methanol, in dehydrated alcohol, practically insoluble in hexane and dichloromethane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5 and approximately 220 hours at pH 7.8.

Pantoprazole Sodium is supplied as a Delayed-Release Tablet, available in two strengths (20 mg and 40 mg). Each Pantoprazole Sodium Delayed-Release Tablet, USP contains 45.11 mg or 22.55 mg of pantoprazole sodium sesquihydrate, USP (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, carnauba wax, ferric oxide yellow, hydroxy propyl cellulose, hypromellose, lactose monohydrate, methacrylic acid copolymer, polyacrylic acid, propylene glycol, sodium carbonate anhydrous, sodium lauryl sulfate, titanium dioxide and triethyl citrate. The tablets are imprinted with opacode black containing ammonium hydroxide, iron oxide black, propylene glycol and shellac. Pantoprazole Sodium Delayed-Release Tablets, (40 mg and 20 mg) complies with USP dissolution test 2.

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

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 to 80 mg) or a single dose of intravenous (30 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 oral 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 in one double-blind crossover study are shown in Table 5.

Table 5: Effect of Single Daily Doses of Oral Pantoprazole on Intra-gastric pH

Time	Placebo	Median pH on day 7		
		20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 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 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole sodium 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 the pretreatment 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 sodium, 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 sodium 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, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1-year study of GERD patients treated with pantoprazole sodium 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 unaltered 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 area under the plasma concentration vs 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.

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.

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. 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 tablet 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)	
	Daytime	Nighttime	Daytime	Nighttime
C _{max} (mcg/mL) ^a	1.8	1.8	1.8	1.8
t _{max} (h) ^b	2.0	2.0	2.0	2.0
AUC (mcg•h/mL) ^c	6.9	5.5	6.9	5.5
CL/F (L/h) ^d	6.6	6.8	6.6	6.8

^a Geometric mean values

^b Median 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 hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day had 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 clopidogrel), nitidipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and propranolol (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 of 79 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 1000 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 MMF. Transplant patients receiving approximately 2000 mg per day of MMF (n=29) 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 MMF 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 (cisapride, theophylline, diazepam [and its active metabolite, desmethyl-diazepam], phenytoin, metoprolol, nitidipine, carbamazepine, midazolam, clarithromycin, diclofenac, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl estradiol]). In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, 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 Pharmacogenetics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (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 3.5 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/*2) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

For known 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 μ 53 \pm transgenic mouse carcinogenicity study was not positive. The 40 mg/kg/day dose of pantoprazole did not induce 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* A552/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 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 (Hetzl-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			Placebo
	10 mg daily (n = 153)	20 mg daily (n = 158)	40 mg daily (n = 162)	150 mg twice daily (n = 68)
4	45.6%*	58.4%#	75.0%**	14.3%
8	66.0%*	83.5%#	92.6%**	39.7%

* ($p < 0.001$) pantoprazole sodium versus placebo

($p < 0.05$) versus 10 mg or 20 mg pantoprazole sodium

($p < 0.05$) versus 10 mg pantoprazole sodium

In this study, all pantoprazole sodium 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 treatment groups. The 40 mg dose of pantoprazole sodium resulted in healing rates significantly greater than those found with either the 20 mg or 10 mg doses.

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

Pantoprazole sodium 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		Nizatidine
	20 mg daily (n = 72)	40 mg daily (n = 70)	150 mg twice daily (n = 70)
4	61.4%*	64.0%*	22.2%
8	79.2%*	82.9%*	41.4%

* ($p < 0.001$) pantoprazole sodium versus nizatidine

Once-daily treatment with pantoprazole sodium 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 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 consumed significantly fewer antacid tablets per day than those taking nizatidine.

Pediatric Patients Ages 5 through 16 Years

The efficacy of pantoprazole sodium in the treatment of EE associated with GERD in pediatric patients ages 5 years through 16 years is 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 (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

The independently conducted, 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 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 40 mg and 20 mg were significantly superior to ranitidine at every timepoint with respect to the maintenance of healing. In addition, pantoprazole sodium 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		Ranitidine	
	20 mg daily	40 mg daily	150 mg twice daily	150 mg twice daily
Study 1	n = 75	n = 74	n = 75	n = 75
Month 1	91*	99*	68	54
Month 3	81*	93*#	59	44
Month 6	76*	90*#	57	44
Month 12	70*	86*#	35	35
Study 2	n = 74	n = 88	n = 84	n = 84
Month 1	89*	92*#	62	47
Month 3	78*	91*#	47	39
Month 6	72*	88*#	37	39
Month 12	72*	83*#	39	39</