PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] TEVA-PANTOPRAZOLE

Pantoprazole Delayed-Release Tablets, 20 mg, 40 mg, Oral
(as pantoprazole sodium sesquihydrate)

Teva Standard

Proton Pump Inhibitor

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RECENT MAJOR LABEL CHANGES

7.0 WARNINGS AND PRECAUTIONS, Immune	09/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Teva-Pantoprazole (pantoprazole sodium sesquihydrate) is indicated for the treatment of conditions where a reduction of gastric acid secretion is required, such as the following:

- Duodenal ulcer
- Gastric ulcer
- Reflux esophagitis
- Symptomatic gastro-esophageal reflux disease (such as, acid regurgitation and heartburn)
- Prevention of gastrointestinal lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs) in patients with a need for continuous NSAID treatment, who have increased risk to develop NSAID-associated upper gastrointestinal lesions.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of pantoprazole sodium in geriatric patients has been established; therefore, Health Canada has authorized all indications for geriatric use (See 4 DOSAGE AND ADMINISTRATION; 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Pantoprazole sodium is contraindicated in patients who are hypersensitive to pantoprazole, substituted benzimidazoles, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Pantoprazole sodium is contraindicated with co-administration of rilpivirine. See 7 WARNINGS AND PRECAUTIONS, Drug Interactions with Antiretroviral Drugs and 9.4 Drug-Drug Interactions.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients should use the lowest dose and shortest duration of proton pump inhibitor (PPI) therapy appropriate to the condition being treated.
- Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.
- For the maintenance treatment of patients with reflux esophagitis and the resolution of symptoms associated with reflux esophagitis, such as heartburn with or without regurgitation, 20 or 40 mg pantoprazole once daily have been used for 3 years in controlled clinical trials. In continuous maintenance treatment, 20 mg pantoprazole has been used in a limited number of patients for up to eight years.

4.2 Recommended Dose and Dosage Adjustment

Duodenal Ulcer

- The recommended adult dose of Teva-Pantoprazole for the oral treatment of duodenal ulcer is 40 mg as pantoprazole given once daily in the morning. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional course of 2 weeks is recommended.

Gastric Ulcer

- The recommended adult oral dose of Teva-Pantoprazole for the oral treatment of gastric ulcer is 40 mg given once daily in the morning. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional course of 4 weeks is recommended.

Symptomatic Gastro-Esophageal Reflux Disease (GERD)

- The recommended adult oral dose for the treatment of symptoms of GERD, including heartburn and regurgitation, Teva-Pantoprazole is 40 mg once daily for up to 4 weeks. If significant symptom relief is not obtained in 4 weeks, further investigation is required.

Reflux Esophagitis

- The recommended adult oral dose of pantoprazole is 40 mg, given once daily in the morning. In most patients, healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.
- Both 20 mg and 40 mg once daily have been demonstrated to be effective in the maintenance of healing of reflux esophagitis. If maintenance therapy fails when using 20 mg once daily, consideration may be given to the 40 mg daily dose as maintenance therapy.

Prevention of Gastrointestinal Lesions Induced by NSAIDs

- The recommended adult oral dose of pantoprazole is 20 mg, given once daily in the

morning.

Geriatrics

- No dose adjustment is recommended for elderly patients. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens. See 10.3 Pharmacokinetics, Special Populations and Conditions.

Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics.

4.4 Administration

Pantoprazole sodium is formulated as an enteric-coated tablet. A whole tablet should not be chewed or crushed, and should be swallowed with fluid in the morning either before, during, or after breakfast.

4.5 Missed Dose

If a dose is forgotten, the missed dose should be taken as soon as possible unless it is close to the next scheduled dose. Two doses should never be taken at one time to make up for a missed dose; patients should just return to the regular schedule.

5 OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. No consistent symptom profile was observed after ingestion of high doses of pantoprazole. Daily doses of up to 272 mg pantoprazole intravenous (i.v.), and single doses of up to 240 mg i.v. administered over 2 minutes, have been administered and were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of overdosage with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients

oral	Delayed Release tablets / 20 mg and 40 mg pantoprazole (as pantoprazole sodium sesquihydrate)	Croscarmellose Sodium, Disodium Phosphate, Hypromellose, Mannitol, Magnesium Stearate, Methacylic acid - ethyl acrylate copolymer, Microcrystalline Cellulose, Sodium Starch Glycolate, Triethyl Citrate, Yellow Iron Oxide.

Teva-Pantoprazole (pantoprazole sodium) is available as delayed-release tablets for oral administration. The delayed-release tablets contain the active ingredient, pantoprazole sodium sesquihydrate, in the form of enteric-coated tablets and are available in two dosage strengths: 45.1 mg pantoprazole sodium sesquihydrate corresponding to 40 mg pantoprazole per tablet and 22.6 mg corresponding to 20 mg pantoprazole per tablet.

Teva-Pantoprazole is available as:
20 mg: Yellow, elliptical, biconvex and smooth tablets, which dimensions are:
Width: 5.85 mm ± 0.29 mm
Length: 8.35 mm ± 0.42 mm.
Available in bottles of 100 tablets.

40 mg: Yellow, elliptical, biconvex and smooth tablets, which dimensions are:
Width: 6.35 mm ± 0.32 mm
Length: 12.00 mm ± 0.60 mm.
Available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

General

Symptomatic response with pantoprazole does not preclude the presence of gastric malignancy.

Clostridium Difficile-Associated Diarrhea

Decreased gastric acidity due to any means, including proton pump inhibitors (PPIs), increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs can lead to an increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile*-associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of co-morbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

Concomitant Use with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose 9.4 Drug-Drug Interactions, methotrexate.

Carcinogenesis and Mutagenesis

Effects of long-term treatment include hypergastrinemia, possible enterochromaffin-like (ECL) cell hyperplasia and carcinoid formation in the stomach, adenomas and carcinomas in the liver and neoplastic changes in the thyroid.

In the rat, the mechanism leading to the formation of gastric carcinoids is considered to be due to the elevated gastrin level occurring during chronic treatment. Similar observations have also been made after administration of other acid secretion inhibitors. For further details, see 16 NON-CLINICAL TOXICOLOGY.

Short-term and long-term treatment with pantoprazole sodium in a limited number of patients up to 6 years have not resulted in any significant pathological changes in gastric oxyntic exocrine cells.

Drug Interactions with Antiretroviral Drugs

PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP2C19. (See 9.4 Drug-Drug Interactions).

Rilpivirine

Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect. See 2 CONTRAINDICATIONS.

Atazanavir and Nelfinavir

Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ® and VIRACEPT® Product Monographs). If the combination of Teva-Pantoprazole with atazanavir is judged unavoidable, close clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of Teva-Pantoprazole should not exceed an equivalent dose of omeprazole of 20 mg daily (see REYATAZ® Product Monograph).

Saquinavir

If Teva-Pantoprazole is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation, are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients (see INVIRASE® Product Monograph).

Endocrine and Metabolism

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. See 8.5 Post-Market Adverse Reactions. In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcaemia and/or hypokalaemia) 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), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

The chronic use of PPIs may lead to hypomagnesemia.

Cyanocobalamin (Vitamin B12) Deficiency

The prolonged use of PPIs may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency (See 9.2 Drug Interactions Overview, Other).

Gastrointestinal

Long-term use of pantoprazole sodium is associated with an increased risk of fundic gland polyps, especially beyond one year. See 8.5 Post-Market Adverse Reactions. Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hepatic/Biliary/Pancreatic

The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg pantoprazole. See 10.3 Pharmacokinetics, Special Populations and Conditions.

Immune

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), 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. Discontinue pantoprazole at the first signs or symptoms of SCARs or other signs of hypersensitivity and consider further evaluation. At the time of prescription, patients should be informed of the signs and symptoms, and advised to monitor closely for skin reactions. See 8.5 Post-Market Adverse Reactions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider

stopping Teva-Pantoprazole. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs. See 8.5 Post-Market Adverse Reactions.

Monitoring and Laboratory Tests

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, Teva-Pantoprazole treatment should be stopped 14 days before CgA measurements. See 9 DRUG INTERACTIONS.

Musculoskeletal

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 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS.

Renal

The daily dose used in renal insufficient patients, as a rule, should not exceed the recommended dosage regimens. See 10.3 Pharmacokinetics, Special Populations and Conditions.

Skin

See 7 WARNINGS AND PRECAUTIONS – Immune.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate or well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity, the potential risk for humans is unknown. Pantoprazole sodium should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus. See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

7.1.2 Breast-feeding

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Pantoprazole sodium should not be given to nursing mothers unless its use is believed to outweigh the potential risks to the infant.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No dose adjustment is recommended based on age. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens. See 10.3 Pharmacokinetics, Special Populations and Conditions.

Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category (> 71 years of age) may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines. See 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Pantoprazole sodium is well tolerated. Most adverse events have been mild and transient showing no consistent relationship with treatment.

The following adverse events (the most frequently reported) have been reported in individuals receiving pantoprazole sodium therapy (40 mg once daily) in controlled clinical trials of at least 6 months duration: Headache (2.1%), Diarrhea (1.6%), Nausea (1.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events have been recorded during controlled clinical investigations in over 13,000 patients exposed to pantoprazole sodium as the single therapeutic agent for treatment of conditions requiring acid suppression. The following adverse reactions considered possibly, probably, or definitely related by the investigator have been reported in individuals receiving pantoprazole therapy (20 mg or 40 mg once daily) in long-term clinical trials (duration of at least 6 months).

Table 2. Adverse drug reactions with a frequency of ≥1 %, related to 40mg pantoprazole, assessed as possibly, probably or definitely related by the investigator

Preferred term	Number of patients	Percentage of patients
Headache	24	2.1
Diarrhea	18	1.6
Nausea	13	1.2

For long-term treatment with 20 mg, no such events were reported with a frequency of more than 1%.

In addition, the following adverse events with a frequency of ≥ 1% considered unrelated, or unlikely related by the investigator have been reported in individuals receiving pantoprazole therapy (20 mg or 40 mg once daily) in short-term and long-term clinical trials.

Table 3. Adverse Events with a frequency of ≥ 1%, 20 or 40 mg pantoprazole sodium

Gastrointestinal Disorders:	Diarrhea
General Disorders:	Influenza like Illness
Nervous System Disorders	Headache

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse drug reactions with a frequency of 0.1 to 1% related to 20 mg pantoprazole are listed below by body system:

Gastrointestinal Disorders:	Diarrhea, Flatulence, Abdominal pain, Abdominal pain upper, Abdominal distension, Gastric polyps, Loose stools, Frequent bowel movements, Eructation, Dyspepsia, Nausea, Vomiting, Constipation
General Disorders:	Fatigue
Hepatobiliary Disorders:	Alanine aminotransferase increased, Aspartate aminotransferase increased, Liver function tests abnormal, Transaminases increased
Laboratory Parameters:	Hyperglycemia
Nervous System Disorders:	Headache, Dizziness, Vertigo
Skin and Subcutaneous Tissue Disorders:	Pruritus, Rash
Special Senses:	Visual disturbance
Other:	Libido decreased

Other adverse drug reactions with a frequency of 0.1 to 1% related to 40 mg pantoprazole are listed below by body system:

Cardiovascular System:	Blood pressure increased, Hypertension, ECG abnormal

Gastrointestinal Disorders:	Flatulence, Abdominal distension, Abdominal pain, Abdominal pain upper, Loose stools, Esophageal reflux aggravated, Gastric polyps, Abdominal discomfort, Abdominal tenderness, Constipation, Eructation, Vomiting, Dyspepsia, Gastroesophageal reflux, Esophagitis
General Disorders:	Fatigue, Peripheral edema, Pyrexia
Hepatobiliary Disorders:	Alanine aminotransferase increased, Aspartate aminotransferase increased, Liver function tests abnormal, Transaminases increased
Laboratory Parameters:	Hypertriglyceridemia
Metabolism and Nutrition Disorders:	Appetite decreased, Weight increase
Nervous System Disorders:	Dysgeusia, Dizziness, Migraine, Vertigo
Respiratory System:	Cough
Skin and Subcutaneous Tissue Disorders:	Pruritus, Rash
Special Senses:	Mouth dry, Vision blurred
Other:	Neoplasm

The following adverse reactions considered possibly, probably, or definitely related by the investigator, reported in individuals receiving pantoprazole therapy (20 mg or 40 mg once daily), in short-term clinical trials (duration of up to 3 months), with a frequency of 0.1 to 1% are listed below by body system:

Gastrointestinal Disorders:	Diarrhea, Flatulence, Nausea, Constipation, Abdominal pain
Nervous System Disorders:	Headache, Dizziness
Skin and Subcutaneous Tissue Disorders:	Pruritus

The following serious adverse events regardless of causality reported with a frequency of <0.1% in either 20 mg or 40 mg pantoprazole sodium once daily are listed below by body system:

Infections and Infestations	Sepsis

In addition the following identified adverse drug reactions have been reported in oral pantoprazole sodium clinical trials in any indication and in any dosage:

SOC	**Uncommon (infrequent): ≥ 1/1,000 to < 1/100 (≥0.1% and <1%);**	**Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)**	**Very rare: <1/10,000 (<0.01%), including isolated reports**
Blood and Lymphatic system Disorders		Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia
Eye Disorders		Disturbances in vision/blurred vision	
Gastrointestinal Disorders	Nausea/vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort		
General Disorders and Administration Site Conditions	Asthenia, fatigue and malaise	Body temperature increased; Edema peripheral	
Hepatobiliary Disorders	Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased	
Immune System Disorders		Hypersensitivity (including anaphylactic	

SOC	Uncommon (infrequent): ≥ 1/1,000 to < 1/100 (≥0.1% and <1%);	Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)	Very rare: <1/10,000 (<0.01%), including isolated
		reactions and anaphylactic shock)	
Metabolism and Nutrition Disorders		Hyperlipidemias and lipid increases (triglycerides, cholesterol); Weight changes	
Musculoskeletal and Connective Tissue Disorders		Myalgia; Arthralgia	
Nervous System Disorders	Headache, Dizziness	Taste disorder	
Psychiatric Disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)
Reproductive System and Breast Disorders		Gynecomastia	
Skin and Subcutaneous Tissue Disorders	Rash/exanthema/eruption; Pruritus	Urticaria; Angioedema	

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Please refer to the Hepatobiliary Disorders and the Laboratory Parameters subsections in 8 ADVERSE REACTIONS. See also 7 WARNINGS AND PRECAUTIONS Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Special Populations and Conditions.

8.5 Post-Market Adverse Reactions

The following adverse events were reported in post-marketing use and causal relation to pantoprazole sodium treatment could not be ruled out. As the events were reported spontaneously, no exact incidences can be provided:

Blood and Lymphatic System Disorders	Eosinophilia
Ear and Labyrinth Disorders	Tinnitus
Eye Disorders	Photophobia

Gastrointestinal Disorders	Pancreatitis; Increased salivation; Microscopic colitis
Hepatobiliary Disorders	Hepatocellular injury; Jaundice; Hepatocellular failure
Investigations	Elevated creatine phosphokinase
Metabolism and Nutrition Disorders	Hyponatremia; Hypomagnesemia; Hypocalcemia*; Hypokalemia*; Increased appetite
Musculoskeletal and Connective Tissue Disorders	Osteoporosis and osteoporosis-related fractures; Rhabdomyolysis
Nervous System Disorders	Anterior ischemic optic neuropathy; Speech disorder; Tremor; Paresthesia
Psychiatric Disorders	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in the case of pre-existence); Nervousness
Renal and Urinary Disorders	Tubulointerstitial nephritis (TIN) (with possible progression to renal failure); Hematuria
Reproductive System and Breast Disorders	Impotence
Skin and Subcutaneous Tissue Disorders	Stevens-Johnson syndrome (SJS); Erythema multiforme; Toxic epidermal necrolysis (TEN; Lyell syndrome); Photosensitivity; Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS; some fatal); Acute generalized exanthematous pustulosis (AGEP)**; Alopecia; Acne; Exfoliative dermatitis

* May be related to the occurrence of Hypomagnesemia

* * See 7 WARNINGS AND PRECAUTIONS, Immune.

There have been post-marketing reports of severe cutaneous adverse reactions (SCARs) and subacute cutaneous lupus erythematosus (SCLE). See 7 WARNINGS AND PRECAUTIONS, Immune.

There have been post-marketing reports of fundic gland polyps (FGPs). See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Pantoprazole undergoes extensive hepatic metabolism via cytochrome P450-mediated oxidation. The main metabolic pathway is demethylation by CYP 2C19 and other metabolic pathways which include oxidation by CYP 3A4. This is followed by sulphate conjugation via a Phase II reaction (non-saturable, non-cytochrome P450 dependent). Pharmacokinetic drug interaction studies in man did not demonstrate the inhibition of the oxidative metabolism of the drug. No induction of the CYP 450 system by pantoprazole was observed during chronic administration of pantoprazole sodium with antipyrine as a marker. Pantoprazole causes long lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of the bioavailability (e.g. ketoconazole, itraconazole, posaconazole, erlotinib)

Other: Generally, daily treatment with any acid-blocking medicines over a long time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature and should be considered if respective clinical symptoms are observed (See 7 WARNINGS AND PRECAUTIONS, Cyanocobalamin (Vitamin B12) Deficiency).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4. Established or potential drug-drug interactions

Concomitant Drug Name	Source of Evidence	Effect	Clinical comment
Antacids	CT	No clinical effect	Concomitant use of antacids does not affect the pharmacokinetics of pantoprazole sodium.

Concomitant Drug Name	Source of Evidence	Effect	Clinical comment
Antiretroviral Drugs	T	↓rilpivirine, atazanavir, nelfinavir ↑saquinavir	See 7 WARNINGS AND PRECAUTIONS, Drug Interactions with Antiretroviral Drugs *Rilpivirine*: Co-administration is contraindicated due to significant decreases in rilpivirine exposure and loss of therapeutic effect. See 2 CONTRAINDICATIONS. *Atazanavir*: Co-administration of TECTA® with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir. (See REYATAZ® Product Monograph). *Nelfinavir*: Co-administration of TECTA® with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and C_{max} for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively). See VIRACEPT® Product Monograph. *Saquinavir*: Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities (see the INVIRASE® Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and C_{max} by 75%.

Concomitant Drug Name	Source of Evidence	Effect	Clinical comment
Methotrexate	C	No clinical effect	Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted. See 7 WARNINGS AND PRECAUTIONS, General, Concomitant Use with Methotrexate
Warfarin	C, CT	↑ INR and PT	No interaction during concomitant administration of warfarin has been observed in clinical pharmacokinetic studies. However, a few isolated cases of changes in INR have been reported in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time (PT)/INR is recommended after initiation, termination or during irregular use of pantoprazole

C = Case Study; CT = Clinical Trial; T = Theoretical; INR = International normalized ratio

Cytochrome P450 Interactions

Pantoprazole sodium does not interact with carbamazepine, caffeine, diclofenac, naproxen, piroxicam, ethanol, glibenclamide, metoprolol, antipyrine, diazepam, phenytoin, nifedipine, theophylline, digoxin, oral contraceptives containing (levonorgestrel and ethinyl oestradiol), or cyclosporine.

9.5 Drug-Food Interactions

Consumption of food does not affect the pharmacokinetics (AUC and C_{max}) of pantoprazole sodium. See 10.3 Pharmacokinetics.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

There have been reports of false-positive results in some urine screening tests for tetrahydrocannabinol (THC) in patients receiving most PPIs, including pantoprazole. A confirmatory method should be considered to verify positive results.

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Teva-Pantoprazole treatment should be stopped 14 days before CgA measurements. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 10.2 Pharmacodynamics, Pharmacodynamic Properties.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Teva-Pantoprazole is a specific inhibitor of the gastric H+, K+-ATPase enzyme (the proton pump) that is responsible for gastric acid secretion by the parietal cells of the stomachPantoprazole is a substituted benzimidazole that accumulates in the acidic environment of the parietal cells after absorption. Pantoprazole is then converted into the active form, a cyclic sulphenamide, which binds selectively to the proton translocating region of the H+, K+-ATPase, thus inhibiting both the basal and stimulated gastric acid secretion. Pantoprazole exerts its effect in an acidic environment (pH < 3), and it is mostly inactive at higher pH. Its pharmacological and therapeutic effect is achieved in the acid-secretory parietal cells. As pantoprazole action is distal to the receptor levels, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (e.g., acetylcholine, histamine, gastrin).

In long-term international studies involving over 800 patients, a 2 to 3 fold mean increase from the pre-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.

10.2 Pharmacodynamics

In clinical studies investigating i.v. and oral administration, pantoprazole sodium inhibited pentagastrin-stimulated gastric acid secretion. With a daily oral dose of 40 mg, inhibition was 51% on Day 1 and 85% on Day 7. Basal 24-hour acidity was reduced by 37% and 98% on Days 1 and 7, respectively.

Pharmacodynamic Properties:

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that PPIs should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Pantoprazole is a potent inhibitor of gastric acid secretion. This was demonstrated with pantoprazole by use of a gastric acid aspiration technique as well as by continuous intragastric pH monitoring. Using the aspiration technique it was also shown that pantoprazole caused a dose-dependent reduction of secreted gastric acid volume.

Table 5. Percent inhibition of pentagastrin-stimulated acid output (PSAO) in healthy volunteers following single oral doses of pantoprazole vs. placebo during 4 to 7 hours post dosing.

Dose	Mean % Inhibition of PSAO

6 mg	13%
10 mg	24%
20 mg	27%
40 mg	42%
60 mg	54%
80 mg	80%
100 mg	82%

With 40 mg administered orally, effective inhibition of gastric acid secretion was achieved. Pantoprazole 40 mg was significantly superior to standard H2-blocker therapy (300 mg ranitidine at night) with regard to median 24-hour and daytime pH; however, not for nighttime measurements.

Table 6. Effects of one week oral treatment in healthy volunteers with placebo, pantoprazole 40 mg in the morning, and standard ranitidine therapy with 300 mg in the evening

Time of Day	**Median pH**		
	Placebo	**Pantoprazole 40 mg**	**Ranitidine 300 mg**
08.00-08.00 (24h)	1.6	4.2*	2.7
08.00-22.00 (Daytime)	1.8	4.4*	2.0
22.00-08.00 (Nighttime)	1.3	3.1	3.7

* $p<0.05$ vs ranitidine

Increasing the once daily dose from 40 mg to 80 mg pantoprazole did not result in a significantly higher median 24-hour pH.

Table 7. Effect of oral pantoprazole in healthy volunteers on median 24-hour pH on Day 7 (40 vs 80 mg).

40 mg	80 mg	
3.8	3.85	n.s.

n.s. =not significant

Hence, once daily administration of 40 mg pantoprazole should be sufficient for the treatment of most patients with acid-related diseases.

10.3 Pharmacokinetics

Table 8. Mean Pharmacokinetic Parameters for Healthy Adult Subjects After a Single Oral Administration of Pantoprazole Sodium

Dose (mg)	C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (µg·h/mL)
40	2.5	2-3	1	5

Pantoprazole shows linear pharmacokinetics, i.e., AUC and C_{max} increase in proportion with the dose within the dose-range of 10 to 80 mg after both i.v. and oral administration. Elimination half-life, clearance and volume of distribution are considered to be dose-independent.

Following repeated i.v. or oral administration, the AUC of pantoprazole was similar to a single dose.

Despite its relatively short elimination half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life. This means that there is no direct correlation between the serum concentrations and the pharmacodynamic action.

Absorption:

Pantoprazole is absorbed rapidly following administration of a 40 mg enteric coated tablet. Its oral bioavailability compared to the i.v. dosage form is 77% and does not change upon multiple dosing. Following an oral dose of 40 mg, C_{max} is approximately 2.5 µg/mL with a t_{max} of 2 to 3 hours. The AUC is approximately 5 µg.h/mL. There is no food effect on AUC (bioavailability) and C_{max}. However, time to reach maximum serum concentrations is slightly increased when the drug is given together with a high caloric breakfast. Taking into account the long duration of action of pantoprazole, which by far exceeds the time period over which serum concentrations are measurable, this observed variation in t_{max} is considered to be of no clinical importance.

Morning administration of pantoprazole was significantly superior to evening dosing with regard to 24 hour intragastric pH, hence morning dosing should be recommended for the treatment of patients. Since the intake of the drug before a breakfast did not influence C_{max} and AUC, which characterize rate and extent of absorption, no specific requirements for intake of pantoprazole in relation to breakfast are necessary.

Distribution:

Pantoprazole is 98% bound to serum proteins. Elimination half-life, clearance and volume of distribution are independent of the dose.

Metabolism:

Pantoprazole is almost completely metabolized in the liver. Studies with pantoprazole in humans reveal no inhibition or activation of the cytochrome P450 (CYP 450) system of the liver.

Pantoprazole undergoes metabolic transformation in the liver. The main serum metabolites (M1-M3) are sulphate conjugates formed after demethylation at the pyridine moiety, the sulphoxide group being either retained (M2, main metabolite), or oxidized to a sulphone (M1), or reduced to a sulphide (M3). These metabolites also occur in the urine (main metabolite M2). Conjugates with glucuronic acid are also found in the urine.

Elimination:

Renal elimination represents the major route of excretion (about 82%) for the metabolites of pantoprazole sodium; the remaining metabolites are excreted in feces. The main metabolite in both the serum and urine is desmethylpantoprazole as a sulphate conjugate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole (approximately 1 hour).

Special Populations and Conditions

- **Pediatrics:**

  No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

- **Geriatrics:**

  An increase in AUC (35%) and C_{max} (22%) for pantoprazole occurs in elderly volunteers when compared to younger volunteers after 7 consecutive days oral dosing with pantoprazole 40 mg. After a single oral dose of pantoprazole 40 mg, an increase in AUC (43%) and C_{max} (26%) occurs in elderly volunteers when compared to younger volunteers. No dose adjustment is recommended based on age. The daily dose in elderly patients, as a rule, should not exceed the recommended dosage regimens.

- **Hepatic Insufficiency:**

  The half-life increased to between 7 and 9 h, the AUC increased by a factor of 5 to 7, and the C_{max} increased by a factor of 1.5 in patients with liver cirrhosis compared with healthy subjects following administration of 40 mg pantoprazole. Similarly, following administration of a 20 mg dose, the AUC increased by a factor of 5.5 and the C_{max} increased by a factor of 1.3 in patients with severe liver cirrhosis compared with healthy subjects.
  Considering the linear pharmacokinetics of pantoprazole, there is an increase in AUC by a factor of 2.75 in patients with severe liver cirrhosis following administration of a 20 mg dose compared to healthy volunteers following administration of a 40 mg dose. Thus, the daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg pantoprazole.

  Renal Insufficiency:

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis, as the difference in AUCs between patients who are dialyzed and those who are not is 4%.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C in the recommended packaging.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

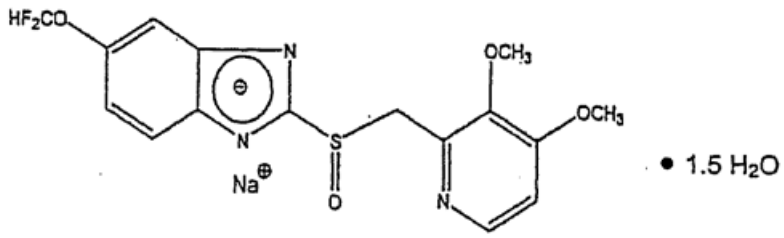
Drug Substance

Common name: pantoprazole sodium sesquihydrate

Chemical name: 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl] benzimidazole, sodium salt, sesquihydrate

Molecular formula and molecular mass: $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$ M_r: 432.4 g/mol

Structural formula:



Physicochemical properties:

Physical description:	White to off-white powder
Solubility:	Freely soluble in water and in ethanol (96%), practically insoluble in hexane.
pka:	8.29
pH [1%w/v Aqueous solution] at about 25°C±2°C:	About 10.59

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Reduction of Gastric Acid Secretion

Symptomatic Gastro-Esophageal Reflux Disease

Table 9. Summary of patient demographics for clinical trials in symptomatic gastro-esophageal reflux disease in adult patients

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
M3-323 (337/2003)	Randomized, double-blind, multicenter, parallel-group comparison	Pantoprazole magnesium: 40 mg, QD, Oral, 4-8 weeks Pantoprazole sodium: 40 mg, QD, Oral, 4-8 weeks	Total=636 Pantoprazole-Mg: 322 Pantoprazole-Na: 314	18-84	Male and Female

Study Results: In a US placebo-controlled study involving 538 patients, 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.

In a second US study involving 215 patients, 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.

Table 10. Summary of patient demographics for clinical trials in prevention of gastrointestinal lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs) in adult patients

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
129/2000	Randomized, double-blind, multicentre, parallel-group comparison in patients 55 years or older with an underlying rheumatic disease that had to be continuously treated with least one NSAID	Pantoprazole 20 mg, 40 mg or omeprazole 20 mg taken QD, Oral, 6 months	Total 595 Pantoprazole 20 mg: 196 Pantoprazole 40 mg: 199 Omeprazole: 200	30-89	Male (172) and female (423)
205/2000	Randomized, double-blind, multicentre, parallel-group comparison in patients 55 years or older with an underlying rheumatic disease that had to be continuously treated with least one NSAID	Pantoprazole 20 mg QD or misoprostol 400 mcg (200 mcg BD), Oral, 6 months	Total = 515 Pantoprazole 257 Misoprostol 258	31-93	Male (139) and female (376)

Trial Design and Study Demographics: Two pivotal studies have been conducted to investigate the effect of pantoprazole sodium in the prevention of the occurrence of endoscopically evident gastrointestinal lesions in patients who, at the start of the study do not present with endoscopically

evident gastrointestinal lesions but who have increased risk to develop NSAID-associated upper gastrointestinal lesions (Table 10).

The following efficacy criteria were used in the studies:

a) Therapeutic failure – Defined as “detection of peptic ulcer and/or more than ten erosions and/or petechiae in the stomach or duodenum, and/or, reflux esophagitis, and/or, adverse event (assessed as 'likely' or 'definitely' related to the study medication), and/or gastrointestinal symptoms leading to premature termination”.

b) Endoscopic failure – Defined as “detection of peptic ulcer, and/or, more than ten erosions/petechiae in the stomach or duodenum, and/or, reflux esophagitis”.

c) Symptomatic failure – Defined as the occurrence of severe gastrointestinal symptoms such as heartburn, epigastric pain, retrosternal feeling of tightness, abdominal pain, eructation of air, acid eructation, pain on swallowing, nausea, retching, vomiting (often collectively referred to as dyspeptic symptoms) including at least “likely” related adverse events of severe intensity concerning the gastrointestinal tract.

Study Results: The results of the studies in patients who require continuous intake of NSAIDs and who have increased risk to develop NSAID-associated gastrointestinal lesions are presented in the Table 11**.**

Table 11. Effect of pantoprazole sodium in prevention of occurrence of endoscopically evident gastrointestinal lesions in patients requiring continuous intake of NSAIDs and who have increased risk to develop NSAID-associated upper gastrointestinal lesions

In remission with regard to Efficacy Criteria:	**Time Interval (months)**	**Study 1; Pantoprazole 20 mg QD(P20) vs pantoprazole 40 mg QD (P40) vs omeprazole 20 mg QD (O20)**			**Study 2; Pantoprazole 20 mg QD (P20) vs misoprostol 200 µg BID (M200)**		
		Remission Rate (%)			**Remission Rate (%)**		
		P20 n = 196	**P40 n = 199**	**O20 n = 200**	**P20 n = 257**	**M200 n = 258**	**p value P20 vs**
Therapeutic failure	0-3	94.2	97.2	93.8	92.5	78.7	**<0.001**
	0-6	89.8	93.1	88.7	89.3	70.3	**<0.001**
Endoscopic failure	0-3	95.9	98.9	96.0	98.0	95.3	0.16
	0-6	91.4	95.3	93.3	94.7	85.7	**0.005**
Symptomatic failure	0-3	98.8	100	98.8	98.5	92.3	**0.004**
	0-6	98.1	100	98.1	98.5	91.7	**0.002**

“In remission” is defined as patients who did not have any of the findings (e.g. “therapeutic failure”, “endoscopic failure”, or symptomatic failure” after 6 months).

Remission rates were obtained by subtracting failures from 100%.

In a six-month study involving 595 patients requiring continuous intake of NSAIDs (Study 129/2000), treatment with pantoprazole 20 mg QD was equivalent to the treatment with pantoprazole 40 mg QD and omeprazole 20 mg QD in this indication.
In a second six-month study involving 515 patients requiring continuous intake of NSAIDs (Study 205/2000), pantoprazole 20 mg was not only equivalent but statistically significantly superior to treatment with misoprostol 200 µg BID with respect to symptomatic and endoscopic findings.

Prevention of Relapse of Reflux Esophagitis

Table 12. Summary of patient demographics for clinical trials in prevention of relapse of reflux esophagitis in adult patients

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
3001A1-302-US	Randomized, double-blind, parallel-group, active-controlled	Pantoprazole 20 mg QD; Pantoprazole 40 mg QD; Ranitidine 150 mg BID Oral 12 months	349	21-81	Male and Female
3001A1-303-US	Randomized, double-blind, parallel-group, active-controlled	Pantoprazole 20 mg QD; Pantoprazole 40 mg QD; Ranitidine 150 mg BID Oral 12 months	371	18-81	Male and Female

Figure 1 - Kaplan-Meier plot; 3001A1-302-US

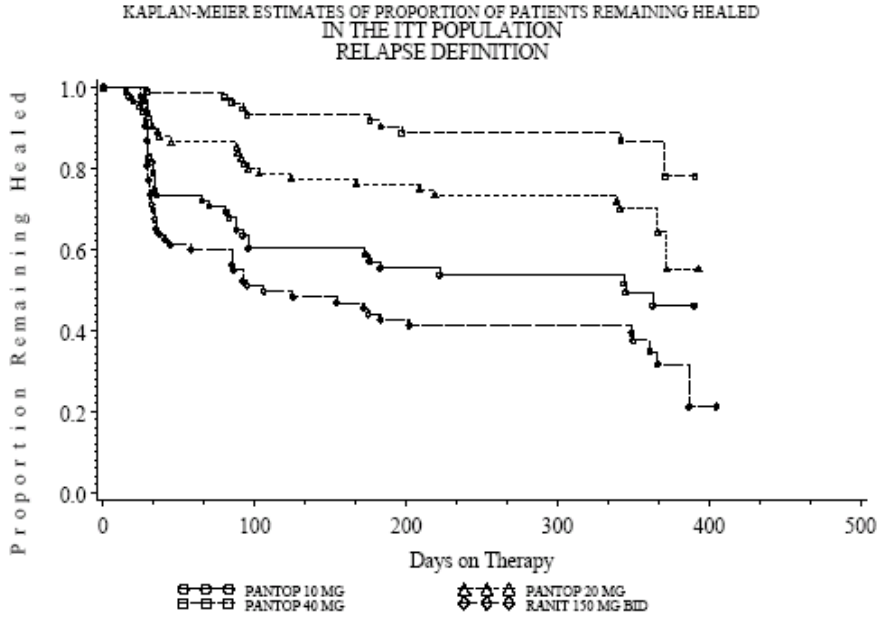
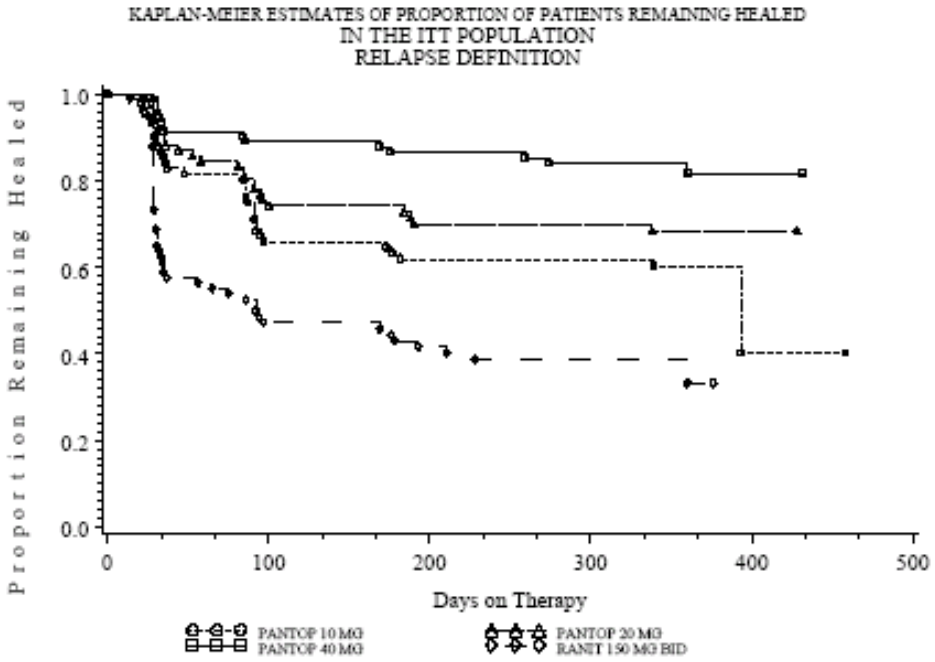


Figure 2 - Kaplan-Meier plot; 3001A1-303-US



In the discrete analysis of the pooled results of the two U.S. studies, 40 mg was significantly (p-value= 0.004) more effective in the maintenance of healed erosive esophagitis compared to 20 mg (see following table).

In the discrete analysis of the pooled results of the two U.S. studies, 40 mg was significantly (p-value = 0.004) more effective in the maintenance of healed erosive esophagitis compared to 20 mg (Table 12).

Table 13. Long-term maintenance of healing of erosive esophagitis: Proportion of patients who relapse in individual studies and pooled studies at 12 months. U.S. Studies

	Pantoprazole 20 mg n/N(%)	Pantoprazole 40 mg n/N(%)	Ranitidine 150 mg n/N(%)
Study 3001A1-302-US			
Month 1	11/86(12.8)*	1/78(1.3)*	32/84(38.1)
Month 3	17/77(22.1)*	5/76(6.6)*	41/81(50.6)
Month 6	21/77(27.3)*	8/70(11.4)*	47/77(61.0)
Month 12	25/75(33.3)*	10/64(15.6)* [a]	52/76(68.4)
Study 3001A1-303-US			
Month 1	11/87(12.6)*	8/93(8.6)*	37/92(40.2)
Month 3	21/80(26.3)*	10/88(11.4)*	45/83(54.2)
Month 6	24/75(32.0)*	12/85(14.1)*	51/79(64.6)
Month 12	25/73(34.2)*	15/78(19.2)*	52/78(66.7)
Pooled data			
Month 12	50/148 (33.8) *	25/142 (17.6) * [a]	104/154 (67.5)

*Statistically significant between treatment and ranitidine at 0.05 level; [a] statistically significant between Pantoprazole 40 mg and 20 mg with adjusted p-value (Holm procedure). Mean age 302-US49: 2 years, 303-US 48: 95 years, 302-US: 28% female / 72% male 303-US: 38% female / 62% male, 302-US: 3.9% black, 4.1% Hispanic, <1% Asian, 91% white, <1% other, US-303: 6.4% black, 6.4% Hispanic, <1% Asian, 86% white, <1% other.

Additionally, long-term maintenance of healing of erosive esophagitis was assessed in two European, randomized, double-blind, parallel-group non-inferiority studies. Eligible patients in both studies had a recent history of grade II or III (Savary-Miller) erosive esophagitis, and endoscopically demonstrated healing. Both studies used as the primary endpoint endoscopically demonstrated recurrence of erosive esophagitis ('relapse'). Pantoprazole 40 mg is non-inferior to pantoprazole 20 mg which means patients who were treated with pantoprazole 40 mg showed no less reduction in the proportion of relapse at 12 months compared to pantoprazole 20 mg (Table 13).

Table 14. Long-term maintenance of healing of erosive esophagitis: Proportion of patients who relapse in individual studies and pooled studies at 12 months. European Studies*

Study	Month	Relapse rates (%)		Diff. Between Treatment and 95%CI (%)
		40 mg Pantoprazole	20 mg Pantoprazole	
FK3028	12	39/174 (22)	45/174 (26)	-3.5 (-12.4;5.5)
FK3033	12	30/151 (20)	49/161 (30)	-10.6 (-20;-1)
Pooled	12	69/325 (21)	94/335 (28)	-6.8 (-13.4;-0.3)

Mean age FK3028 56 years, FK3033 50 years, FK3028 35% female / 65% male, FK3033: 28% female / 72% male.

* These studies were performed between 1993 – 1997.

14.3 Comparative Bioavailability Studies

A double blind, randomized, single-dose, two-period, two-way crossover bioequivalence study of Teva-Pantoprazole delayed-release tablets, 40 mg (Teva Canada Limited) and PANTOLOC® enteric-coated tablets, 40 mg (Takeda Canada Inc.) administered as a single 1 x 40 mg dose was conducted in healthy adult human male subjects (N=40) under fasting conditions. The comparative bioavailability data based on 39 subjects who completed the study are summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pantoprazole sodium (1x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	14777.92 17001.62 (51.48)	15205.97 17605.17 (52.63)	97.2	88.9 - 106.3
AUC_I (ng•h/mL)	17688.60 22478.92 (70.46)	18193.46 23353.40 (74.96)	97.2	88.8 - 106.5
C_{MAX} (ng/mL)	3973.26 4213.42 (32.34)	4359.72 4652.01 (29.63)	91.1	81.8 - 101.5
T_{MAX}[3] (h)	3.50 (2.00-6.00)	2.68 (1.67-5.07)		
$T_{½}$[4] (h)	3.35 (62.25)	3.52 (70.33)		

1 Teva-Pantoprazole (pantoprazole as pantoprazole sodium) delayed-release tablets, 40 mg (Teva Canada Limited).
2 PANTOLOC® (pantoprazole as pantoprazole sodium) enteric-coated tablets, 40 mg (Takeda Canada Inc.).
3 Expressed as the median (range) only
4 Expressed as the arithmetic mean (CV%) only

A double blind, randomized, single-dose, two-period, two-way crossover, bioequivalence study of Teva-Pantoprazole delayed-release tablets, 40 mg (Teva Canada Limited) and PANTOLOC® enteric-coated tablets, 40 mg (Takeda Canada Inc.), administered as a single 1 x 40 mg dose, was conducted in healthy adult human male subjects (N=80) under fed conditions. The comparative bioavailability data based on 73 subjects who completed the study are summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pantoprazole sodium (1 x 40 mg) From measured data Geometric Mean Arithmetic Means (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	11376.88 14005.40 (68.43)	11730.08 14338.55 (67.97)	97.0	89.2 - 105.5
AUC_I [3] (ng•h/mL)	12191.55 18119.04 (101.45)	12547.27 16930.49 (81.39)	97.2	93.0 - 101.5
C_{max} (ng/mL)	3479.65 3628.88 (29.88)	4141.04 4298.89 (27.78)	84.0	79.8 - 88.5
T_{max}[4] (h)	6.50 (2.00-24.00)	6.00 (2.00-24.02)		
$T_{½}$[3,5] (h)	3.91 (130.58)	3.05 (78.41)		

1 Teva-Pantoprazole (pantoprazole as pantoprazole sodium) delayed-release tablets (Teva Canada Limited).
2 PANTOLOC® (pantoprazole as pantoprazole sodium) enteric-coated tablets 40 mg (Takeda Canada Inc.).
3 N=65
4 Expressed as the median (range) only
5 Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

In acute toxicity studies in mice, the mean lethal dose (LD_{50}) values for pantoprazole were found to be around 390 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.

In the rat, the corresponding values were around 250 mg/kg for i.v. administration and greater than 1000 mg/kg for oral administration.

Acute toxicity studies were conducted on B8810-044, the major degradation product of pantoprazole. The approximate LD_{50} values for mice (119-167 mg/kg) and rats (73-82 mg/kg) were lower than those for pantoprazole itself, after intravenous injection, but the toxic symptoms were similar to those noted for the drug. A 4-week repeat dose study was also conducted using this degradation product using the i.v. route in rats. Rats received 5 and 25 mg of B8810-044/kg, while a comparison group received 25 mg/kg of pantoprazole.
Muscle twitches were observed immediately after injection in rats receiving 25 mg/kg of the degradation product, but not in the pantoprazole-treated animals. Otherwise the compounds were comparable.

Table 16. Acute toxicity studies of pantoprazole

Species	Sex	Route	ca. LD_{50}* (mg/kg)
Mouse	M	p.o.	>1000
	F	p.o.	747
	M	i.v.	399
	F	i.v.	395
Rat	M	p.o.	1343
	F	p.o.	1037
	M	i.v.	330
	F	i.v.	343
Dog	M/F	p.o.	300-1000**
	M/F	i.v.	150-300

* Doses refer to the sodium salt administered in solution

** sodium salt as dry powder in gelatine capsules

The symptoms seen after lethal oral or i.v. doses were similar in rats and mice: the animals displayed ataxia, reduced activity, hypothermia and prostration. Surviving animals recovered uneventfully. Salivation, tremor, lethargy, prostration and coma were seen in dogs at lethal oral doses, with death occurring on the following day. Ataxia, tremor and a prone position were noted at sublethal oral and i.v. doses, but the survivors recovered quickly and appeared fully normal after the 2-week observation period.

Chronic Toxicity

Daily oral doses of pantoprazole in 1- and 6-month SD rat repeated-dose studies were 1, 5, 20, and 500 mg/kg and 0.8, 4, 16 and 320 mg/kg, respectively; doses for a 1 month rat i.v. study were 1, 5, and 30 mg/kg.

A 12-month toxicity study in SD rats was conducted using daily oral doses of 5, 50, and 300 mg/kg. Daily oral doses in 1- and 6 month (beagle) dog studies were 7.5, 15, 30, and 100 mg/kg and 5, 15, 30, and 60 mg/kg respectively. In a 12-month oral study in dogs, 2.5, 15, and 60 mg/kg were administered daily.

Hypergastrinemia was dose-related and was observed at all doses investigated in the studies mentioned above, but was reversible upon cessation of treatment. Drug-related effects on the stomach included increased stomach weights and morphologic changes of the mucosa. In the 6-month rat study, increased stomach weight and some cellular changes were detected at all doses. In the 1-month rat study, gastric changes were detected at 5 mg/kg but not at 1 mg/kg. In dogs, increased stomach weight was observed at all doses studied. There were no gastric cellular changes detected at oral doses of 7.5 or 5 mg/kg in the 1- and 6-month dog studies, respectively. In both species, most gastric effects were reversible after a 4- or 8-week recovery

period. Hypergastinemia and gastric changes were considered to be the consequence of the pharmacological action of the compound, namely prolonged and profound inhibition of acid secretion.

Increased liver weight in the rat experiments was considered to be a consequence of the induction of hepatic drug metabolizing systems and was found to be associated with centrilobular hepatocellular hypertrophy at 320 mg/kg in the 6-month study and at 50 and 300 mg/kg after 12 months of treatment. Increased liver weights were also detected at a dose of 16 mg/kg in male rats in the 6-month study and at 500 mg/kg, but not 20 mg/kg, in the 1- month study. Increased liver weight was noted in male dogs of all dose groups in the 1-month study, though only at 100 mg/kg in females on the same study. Both males and females had increased liver weights after 6 months administration of 30 or 60 mg/kg, but not of 15 mg/kg. In the 12-month study, liver weights were increased only in the female dogs dosed with 60 mg/kg. There were no hepatic lesions that correlated with increased liver weight in the dog studies. In dogs, the increase in liver weight was attributed to an activation of hepatic drug metabolizing systems as mentioned for rats.

Thyroid activation in animal experiments is due to the rapid metabolization of thyroid hormones in the liver and has been described in a similar form for other drugs. Thyroid weights were increased in both sexes at 500 mg/kg in the 1-month rat study and at 320 mg/kg in the rat 6-month study. Thyroid follicular cell hypertrophy was noted in females at these doses, in rats treated with 50 and 300 mg/kg in the 12 month study and also in a few females at 16 mg/kg in the 6 month study. There were no thyroid effects in rats at or below an oral dose of 5 mg/kg even after 1 year. In the dog, no effects were seen on the thyroid after 4 weeks. Only slight, but not dose-dependent, increases in thyroid weights were seen after 6 months, but no changes were observed histologically. In the 12 month study, the relative thyroid weights in the 60 mg/kg group were only slightly higher than those of the control dogs, and changes were detected histologically in only a few animals under 15 and 60 mg/kg. In both species, changes were reversible.

Increased serum cholesterol values were noted in all groups in the 6- and 12 month dog studies and in all groups in the 12 month rat study. The increases were slight and were reversible after cessation of treatment.

In dog studies, oral doses of pantoprazole of 15 mg/kg or above caused a transient pulmonary edema in a proportion of naive dogs during the first week of drug administration. Pulmonary edema caused death in a few dogs after repeated oral doses of 15 mg/kg or above. There is strong evidence that the pulmonary toxicity is due to a thiol metabolite which does not occur in man. No evidence of pulmonary edema was detected in dogs at an oral dose of 7.5 mg/kg nor at 60 mg/kg when administered daily for 6 or 12 months after a 1 week dose escalation phase.**Carcinogenicity:**

Three carcinogenicity studies had been conducted with pantoprazole:

- A 24 month oral study was conducted at doses of 0.5, 5, 50 and 200 mg/kg/day in SD rat.
- A 24 month oral study was conducted at doses of 5, 15 and 50 mg/kg/day in Fischer-344 rat.
- A 24 month oral study was conducted at doses of 5, 25 and 150 mg/kg/day in B6C3F1 mouse.

Pantoprazole, dissolved in distilled water, was administered once a day by oral gavage to groups of 50 male and 50 female B6C3F1 mice at doses of 5, 25, or 150 mg/kg. An identical control group was dosed with distilled water (pH 10), while a second identical control group received no treatment at all. In the first rat study, pantoprazole was administered once a day by oral gavage to groups of 70 male and 70 female SD rats at doses of 0.5, 5, 50, and 200 mg/kg. A control group of 70 males and 70 females received the vehicle. In the second rat study, pantoprazole was administered once a day by oral gavage to groups of 50 male and 50 female Fischer-344 rats at doses of 5, 15, and 50 mg/kg. A control group of 50 males and 50 females received the vehicle, while another group remained untreated.

In the first 2 year carcinogenicity study in rats, which corresponds to a lifetime treatment for rats, neuroendocrine neoplasms were found in the stomach at doses of 50 mg/kg/day and above in males and at 0.5 mg/kg/day and above in females. Tumor formation occurred late in the life of the animals (only after 17 months treatment), whereas no tumors were found in rats treated with an even higher dose for 1 year. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated, and it is considered to be due to high levels of serum gastrin observed in the rat during chronic treatment. In the second rat carcinogenicity study, neuroendocrine cell tumors in the stomach were found in all treated female groups and in the male 15 and 50 mg/kg groups. No metastases from any gastric neuroendocrine cell tumours were detected.

ECL-cell neoplasms were not observed in either the carcinogenicity study in the mouse (24 months) or in the chronic studies in the dog. In clinical studies, where pantoprazole was administered at doses up to 80 mg, ECL-cell density remained almost unchanged.

Microscopy of the rat (first carcinogenicity study) and mouse tissues gave evidence for an increase in liver tumors. In the rat experiment, the incidence of benign liver tumors in the 50 and 200 mg/kg groups and the incidence of hepatocellular carcinoma was increased in the males and females of the 200 mg/kg group. There was a slightly higher incidence of hepatocellular adenomas and carcinomas in the female mice of the 150 mg/kg group than in either of the 2 control groups. Other changes in the liver morphology were present as well. Centrilobular hepatocellular hypertrophy increased in incidence and severity with increasing dose, and hepatocellular necrosis was increased in the highest dose in the rat studies and in the mouse study. Hepatocellular tumors are common in mice, and the incidence found for the female 150 mg/kg group was within historical control ranges for this strain. The liver tumor incidences in rats treated with 50 mg/kg and in the male rats treated with 200 mg/kg were also within historical control incidences for the rat. These tumors occurred late in the life of the animals and were primarily benign. The nongenotoxic mechanism of rodent liver tumor formation after prolonged treatment with pantoprazole is associated with enzyme induction leading to hepatomegaly and centrilobular hypertrophy and is characterized by tumor induction in low incidences at high doses only. As pantoprazole acts in a similar fashion to phenobarbital, causing reversible centrilobular hepatocellular hypertrophy and enzyme induction in short-term studies, it is probable that the mechanism of action for induction of the liver tumors seen in long-term rodent studies is also the same. Hepatocellular tumors at high doses in rodents are not indicative of human carcinogenic risk.

A slight increase in neoplastic changes of the thyroid was observed in rats receiving

pantoprazole at 200 mg/kg/day. The incidences of these tumours were within the historical control ranges for this rat strain. No thyroid neoplasms were observed in the 12-month study. The no-effect dose for both male and female rats is 50 mg/kg, which is 100 times the most commonly used human dose (i.e. 40 mg dose). The effect of pantoprazole on the thyroid is secondary to the effects on liver enzyme induction, which lead to enhanced metabolism of thyroid hormones in the liver. As a consequence, increased TSH is produced, which has a trophic effect on the thyroid gland. Clinical studies have demonstrated that neither liver enzyme induction nor changes in thyroid hormonal parameters occur in man after therapeutic doses of pantoprazole.

Tumors induced in rats and mice by pantoprazole were the result of nongenotoxic mechanisms which are not relevant to humans. Tumors were induced in rodents at dosages that provide higher exposure than with human therapeutic use. Based on kinetic data, the exposure to pantoprazole in rats receiving 200 mg/kg was 22.5 times higher than that found in humans receiving 40 mg oral doses. In mice receiving 150 mg/kg, exposure to pantoprazole was 2.5 times higher than that in humans.

Genotoxicity:

Pantoprazole was studied in several mutagenicity studies: Pantoprazole was found negative in the Ames test, an in vivo chromosome aberration assay in rat bone marrow, a mouse lymphoma test, two gene mutation tests in Chinese hamster ovary cells in vitro, and two micronucleus tests in mice in vivo. Pantoprazole was found positive in three of four chromosome aberration assays in human lymphocytes in vitro. The in vitro tests were conducted both in the presence and absence of metabolic activation. The potential of pantoprazole to induce DNA repair synthesis was tested negative in an in vitro assay using rat hepatocytes. In addition, a rat liver DNA covalent binding assay showed no biologically relevant binding of pantoprazole to DNA.

In addition, two in vitro cell transformation assays using different cell types were performed to aid in the interpretation of the rodent carcinogenicity studies; in neither test did pantoprazole enhance the morphologic transformation of the cell types used.

A bacterial mutation assay conducted with the degradation product B8810-044, gave no indication of a mutagenic potential.

Reproductive and Developmental Toxicology:

Pantoprazole was not teratogenic to rats or rabbits at doses up to 450 and 40 mg/kg/day (gavage), 20 and 15 mg/kg/day (i.v. injection), respectively.

Treatment of male rats with pantoprazole up to 500 mg/kg p.o. for 127 days did not affect fertility. Treatment of pregnant rats induced dose-dependent fetotoxic effects: increased pre- and postnatal deaths (450 mg/kg/day), reduced fetal weight and delayed skeletal ossification (150 mg/kg/day), and reduced pup weight (15 mg/kg/day). These results may be explained by maternal toxicity of pantoprazole at high dose and/or placental transfer of pantoprazole.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the fetus is increased

shortly before birth regardless of the route of administration.

In a peri-postnatal rat reproduction study designed to assess bone development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were observed at exposures (C_{max}) approximately 2x the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups and body weights were also trending toward reversibility after a drug-free recovery period. The increased mortality has only been reported in pre-weaning rat pups (up to 21 days age) which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous peri-postnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study. Investigations revealed no evidence of impaired fertility or teratogenic effects.

In humans, there are no adequate or well-controlled studies with the use of pantoprazole during pregnancy.

Non-clinical Pharmacodynamics

In vivo, pantoprazole produced marked and long-lasting inhibition of basal and stimulated gastric acid secretion with median effective dose (ED_{50}) values ranging from 0.2 -2.4 mg/kg in rats and dogs. In addition to the administration of single doses, pantoprazole has been tested upon repeated oral administration (e.g. during 24-h pH-metry in dogs performed under pentagastrin stimulation). While a dose of 1.2 mg/kg did not significantly elevate pH on Day 1, pH rose to values between 4 and 7 after a 5-day dosing regimen. This effect was no longer observed 18 hours after the last drug administration. In various gastric ulcer models in the rat, pantoprazole showed antiulcer activity.

In parallel to the profound inhibition of gastric acid secretion, pantoprazole induced a dose-dependent increase in serum gastrin levels up to values above 1000 pg/mL from a control level of about 100 pg/mL. As a consequence of persisting hypergastrinemia in rats after high/doses of pantoprazole, hyperplastic changes were observed in the fundic mucosa with an increased density of enterochromaffin-like (ECL) cells. These changes were reversible during drug-free recovery periods.

In a battery of standard high-dose pharmacology tests, no influence of pantoprazole was detected on the central and peripheral nervous system. In conscious dogs as well as anaesthetized cats receiving single i.v. doses up to 10 mg/kg pantoprazole, no consistent changes with respect to respiratory rate, ECG, EEG, blood pressure and heart rate were observed. Higher doses led to modest and transient reductions in blood pressure and variable changes in heart rate. No influence of pantoprazole was found on renal function and on autonomic functions, such as pancreatic and bile secretion, gastrointestinal motility and body temperature. No consistent changes in the effects of ethanol, pentobarbitone, or hexobarbitone were induced by pantoprazole; only doses over 300 mg/kg prolonged the effects of diazepam.

Non-clinical Pharmacokinetics

Absorption and Distribution:

Pantoprazole is absorbed rapidly in both rat and dog. Peak plasma levels are attained within 15

to 20 minutes in the rat and after about 1 hour in the dog. Oral bioavailability is 33% in the rat and 49% in the dog. Following absorption, autoradiography and quantitative tissue distribution experiments have shown that pantoprazole is rapidly distributed to extravascular sites. Following administration of pantoprazole, distribution of radioactivity in the blood and most organs is found to be uniform initially. After 16 hours, radiolabelled pantoprazole is predominantly detected in the stomach wall. After 48 hours, all the administered radioactivity is found to have been excreted. Penetration of the blood-brain barrier by radiolabelled pantoprazole is very low. Protein binding in the rat and dog is 95% and 86%, respectively.

Metabolism and Elimination:

Pantoprazole is extensively metabolized. Oxidations and reductions at different sites of the molecule, together with Phase II reactions (sulfation and glucuronidation) and combinations thereof result in the formation of various metabolites. In rats and dogs, 29-33% of a pantoprazole dose is excreted as urinary metabolites, and the remainder as biliary/fecal metabolites. Almost no parent compound can be found in the excreta.

Mammoglandular passage and transplacental transport has been investigated in the rat using radiolabelled pantoprazole. A maximum of 0.23% of the administered dose is excreted in the milk. Radioactivity penetrates the placenta with 0.1-0.2% of the dose /g fetal tissue on the first day after oral administration.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PANTOLOC® (Pantoprazole Enteric-Coated Tablets, 20 mg and 40 mg), submission control 266961, Product Monograph, Takeda Canada Inc. (MAR 30, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] TEVA-PANTOPRAZOLE

Pantoprazole Delayed-Release Tablets (as pantoprazole sodium sesquihydrate)

Read this carefully before you start taking **Teva-Pantoprazole** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Teva-Pantoprazole**.

What is Teva-Pantoprazole used for?

Teva-Pantoprazole is used to treat stomach acid related problems. This includes:

- **Stomach ulcer.**
  A stomach ulcer is a sore on the lining of the stomach. This is also known as a gastric ulcer.
- **Duodenal ulcer.**
  A sore on the lining of the duodenum. The duodenum is the first part of the small intestine.
- **Reflux esophagitis.**
  This is a severe form of heartburn.
- **Symptoms of gastro-esophageal reflux disease (GERD).**
  The symptoms include heartburn and acid regurgitation. GERD is a condition in which stomach acid backs up into your esophagus.
- **When taking non-steroidal anti-inflammatory drugs (NSAIDs).**
  Stops stomach and duodenal ulcers from forming.

How does Teva-Pantoprazole work?

Teva-Pantoprazole is a proton pump inhibitor. It reduces the amount of acid your stomach makes.

What are the ingredients in Teva-Pantoprazole?

Medicinal ingredients: pantoprazole sodium sesquihydrate.

Non-medicinal ingredients: Croscarmellose Sodium, Disodium Phosphate, Hypromellose, Mannitol, Magnesium Stearate, Methacylic acid - ethyl acrylate copolymer, Microcrystalline Cellulose, Sodium Starch Glycolate, Triethyl Citrate, Yellow Iron Oxide.

Teva-Pantoprazole comes in the following dosage forms:

- Tablet, 20 mg and 40 mg.

Do not use Teva-Pantoprazole if:

- You are allergic to any of its ingredients. (See **What are the ingredients in Teva-Pantoprazole?**);
- You are taking rilpivirine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Teva-Pantoprazole. Talk about any health conditions or problems you may have, including if you:

- are taking other medications (see **The following may interact with Teva-Pantoprazole)**.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breast feed. Pantoprazole has been found in human breast milk. Talk with your doctor.
- have a history of liver problems
- have low magnesium in the body, which may cause symptoms such as:
  - rapid heartbeat.
  - dizziness, seizures.
  - muscle cramping, twitches or spasms.
- are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:

Tell your doctor if you experience the following symptoms before taking Teva-Pantoprazole:

- unexplained weight loss.
- severe or persistent diarrhea.
- repeated vomiting.
- vomiting blood.
- dark stools.
- tiredness (anemia).
- difficulty in swallowing.

You should take Teva-Pantoprazole exactly as prescribed. You will use the lowest dose and shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

Depending on your condition, your doctor may tell you to use this type of medicine (proton pump inhibitors) for a longer period.

Using proton pump inhibitors for a long time (every day for a year or longer) may increase risks of broken bones of the hip, wrist or spine. Talk to your doctor about this risk.

Long term use of proton pump inhibitors may interfere with the absorption of Vitamin B12 from the diet. This may cause a shortage of Vitamin B12 in your body. Talk to your doctor.

Using Teva-Pantoprazole for a long period of time may cause a growth in your stomach (polyp), especially after one year.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact Teva-Pantoprazole:

- warfarin
- atazanavir
- methotrexate
- itraconazole
- erlotinib
- nelfinavir
- saquinavir/ritonavir
- ketoconazole
- posaconazole

How to take Teva-Pantoprazole:

- Take Teva-Pantoprazole in the morning.
  - with or without food
  - with breakfast, is recommended

- Swallow the tablet(s) whole with water.
- Do not crush or chew the tablet(s).

Usual adult dose:

Your doctor will have told you what dose to take for your condition. Follow your doctor's directions carefully as they may be different from the information provided in this leaflet.

Overdose:

If you think you, or a person you are caring for, have taken too much Teva-Pantoprazole, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose. Take the next dose at your regular time. Do not double doses.

What are possible side effects from using Teva-Pantoprazole?

Like all medicines, Teva-Pantoprazole may cause side effects. Side effects have generally been mild and did not last a long time. These are not all the possible side effects you may have when taking Teva-Pantoprazole. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects are:

- headache
- diarrhea
- nausea

Tell your doctor right away if you have any of these symptoms:

- new or worsening joint pain
- rash on your cheeks or arms that gets worse in the sun

Your symptoms may get worse after stopping your medication. This may occur as your stomach may increase the production of acid.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Disturbances in vision. Most cases reported are not serious.			✓
UNKNOWN			
Liver damage. Symptoms include a yellow tinge to the skin and eyes.			✓
Severe Cutaneous Adverse Reactions (SCAR) (Severe Skin Reactions): Skin rash which may have blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet). You may also experience fever, chills, body aches, shortness of breath, or enlarged lymph nodes.			✓
Muscle wasting.			✓
Clostridium difficile colitis (bowel inflammation). Symptoms include severe (watery or bloody) diarrhea, fever, and abdominal pain or tenderness.			✓

Microscopic colitis (inflammation of the gut). Symptoms include chronic watery diarrhea, abdominal pain, cramps or bloating, weight loss, nausea, uncontrollable bowel movement, signs of dehydration such as extreme thirst, less frequent urination, dark-coloured urine, fatigue, dizziness, confusion. The symptoms of microscopic colitis can come and go frequently. If you have watery diarrhea that lasts more than a few days, contact your doctor.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Teva-Pantoprazole at room temperature, 15°- 30°C.

Keep out of reach and sight of children.

If you want more information about Teva-Pantoprazole:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited.

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