

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup> **Bio-PANTOPRAZOLE**

Pantoprazole Sodium Delayed-Release Tablets  
Delayed-Release Tablets, 20 mg and 40 mg pantoprazole  
(as pantoprazole sodium sesquihydrate), Oral,  
USP  
Proton Pump Inhibitor

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## RECENT MAJOR LABEL CHANGES

### TABLE OF CONTENTS

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

RECENT MAJOR LABEL CHANGES .....	2
TABLE OF CONTENTS.....	2
<b>PART I: HEALTH PROFESSIONAL INFORMATION .....</b>	<b>4</b>
<b>1 INDICATIONS.....</b>	<b>4</b>
1.1 Pediatrics (< 18 years of age) .....	4
1.2 Geriatrics .....	4
<b>2 CONTRAINDICATIONS .....</b>	<b>4</b>
<b>4 DOSAGE AND ADMINISTRATION .....</b>	<b>5</b>
4.1 Dosing Considerations .....	5
4.2 Recommended Dose and Dosage Adjustment .....	5
4.4 Administration .....	6
4.5 Missed Dose .....	6
<b>5 OVERDOSAGE.....</b>	<b>6</b>
<b>6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING .....</b>	<b>7</b>
<b>7 WARNINGS AND PRECAUTIONS.....</b>	<b>8</b>
7.1 Special Populations .....	11
7.1.1 Pregnant Women.....	11
7.1.2 Breast-feeding .....	11
7.1.3 Pediatrics.....	11
7.1.4 Geriatrics .....	11
<b>8 ADVERSE REACTIONS .....</b>	<b>12</b>
8.1 Adverse Reaction Overview.....	12
8.2 Clinical Trial Adverse Reactions.....	12
8.3 Less Common Clinical Trial Adverse Reactions .....	13
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data .....	15
8.5 Post-Market Adverse Reactions .....	15

<b>9</b>	<b>DRUG INTERACTIONS .....</b>	<b>16</b>
9.2	Drug Interactions Overview .....	16
9.4	Drug-Drug Interactions .....	17
9.5	Drug-Food Interactions .....	20
9.6	Drug-Herb Interactions.....	20
9.7	Drug-Laboratory Test Interactions.....	20
<b>10</b>	<b>CLINICAL PHARMACOLOGY .....</b>	<b>20</b>
10.1	Mechanism of Action .....	20
10.2	Pharmacodynamics .....	21
10.3	Pharmacokinetics .....	23
<b>11</b>	<b>STORAGE, STABILITY AND DISPOSAL.....</b>	<b>25</b>
<b>12</b>	<b>SPECIAL HANDLING INSTRUCTIONS .....</b>	<b>25</b>
<b>PART II: SCIENTIFIC INFORMATION .....</b>		<b>26</b>
<b>13</b>	<b>PHARMACEUTICAL INFORMATION .....</b>	<b>26</b>
<b>14</b>	<b>CLINICAL TRIALS .....</b>	<b>27</b>
14.1	Trial Design and Study Demographics.....	27
14.2	Study Results.....	29
14.3	Comparative Bioavailability Studies.....	35
<b>15</b>	<b>MICROBIOLOGY .....</b>	<b>36</b>
<b>16</b>	<b>NON-CLINICAL TOXICOLOGY .....</b>	<b>36</b>
<b>17</b>	<b>SUPPORTING PRODUCT MONOGRAPHS.....</b>	<b>41</b>
<b>PATIENT MEDICATION INFORMATION.....</b>		<b>42</b>

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Bio-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.
- *Helicobacter pylori* associated duodenal ulcer

Pantoprazole, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with an active duodenal ulcer who are *H. pylori* positive. Clinical trials using combinations of pantoprazole with appropriate antibiotics have indicated that such combinations are successful in eradicating *H. pylori*. (see [14 CLINICAL TRIALS](#) and [4 DOSAGE AND ADMINISTRATION](#), for more information.)

#### 1.1 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 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 Bio-PANTOPRAZOLE (pantoprazole sodium sesquihydrate) 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 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.

#### *Helicobacter pylori* associated duodenal ulcer

- Pantoprazole/Clarithromycin/Metronidazole Triple Combination Therapy: The recommended dose for *H. pylori* eradication is treatment for seven days with Bio-PANTOPRAZOLE 40 mg together with clarithromycin 500 mg and metronidazole 500 mg, all twice daily.
- Pantoprazole/Clarithromycin/Amoxicillin Triple Combination Therapy: The recommended dose for *H. pylori* eradication is treatment for seven days with Bio-PANTOPRAZOLE 40 mg together with clarithromycin 500 mg and amoxicillin 1000 mg, all twice daily.
- When Bio-PANTOPRAZOLE (pantoprazole sodium sesquihydrate) is prescribed in combination with clarithromycin, amoxicillin or metronidazole for the eradication of an *H. pylori* infection, the Product Monograph for the antibiotics used should be consulted and followed.

#### Symptomatic gastro-esophageal reflux disease (GERD)

- The recommended adult oral dose for the treatment of symptoms of GERD, including heartburn and regurgitation, 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](#).

## 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 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 Tablet, 20 and 40 mg pantoprazole (as pantoprazole sodium sesquihydrate)	Calcium stearate, colloidal silicon dioxide, crospovidone, mannitol, hydroxypropylmethyl cellulose, polyethylene glycol, sodium carbonate anhydrous, sodium starch glycollate, sodium hydroxide, Eudragit (contains: methacrylic acid-ethyl acrylate copolymer, sodium lauryl sulfate and polysorbate), opadry yellow (contains: lecithin (soy), titanium dioxide, yellow iron oxide, polyvinyl alcohol, talc and xanthan gum), imprinting ink (contains Shellac, isopropyl alcohol, black iron oxide, n-butyl alcohol, propylene glycol and ammonium hydroxide)

Bio-PANTOPRAZOLE (pantoprazole sodium) is available as delayed-release tablets for oral administration.

Bio-PANTOPRAZOLE 20 mg tablets are yellow colored, oval, biconvex enteric coated tablets '20' printed in black on one side and plain on other side. Each tablet contains 20 mg pantoprazole (22.6 mg pantoprazole sodium sesquihydrate).

Bio-PANTOPRAZOLE 40 mg tablets are yellow colored, oval, biconvex enteric coated tablets 'P40' printed in black on one side and plain on other side. Each tablet contains 40 mg pantoprazole (45.1 mg pantoprazole sodium sesquihydrate).

Bio-PANTOPRAZOLE 20 mg tablets are available in bottles of 100 tablets.

Bio-PANTOPRAZOLE 40 mg tablets are available in bottles of 100 tablets and 500 tablets, and blister packs of 3x10's tablets.

## 7 WARNINGS AND PRECAUTIONS

### General

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anemia, or melena) and when gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Bio-PANTOPRAZOLE (pantoprazole sodium sesquihydrate) is instituted since treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis. Further investigation should be considered if symptoms persist despite adequate treatment. In long-term treatment, patients should be kept under regular surveillance.

### *Antibiotic Combination Therapy*

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis”.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

### *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 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 CYP 2C19 (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 Atazanavir and Nelfinavir Product Monographs).

If the combination of Bio-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 Bio-PANTOPRAZOLE should not exceed an equivalent dose of omeprazole of 20 mg daily (see Atazanavir Product Monograph).

### *Saquinavir*

If Bio-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 Saquinavir 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 hypokalemia) 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 proton pump inhibitors 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 & Renal**

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](#).

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](#).

Pantoprazole should not be used in combination treatment for the eradication of *H. pylori* in patients with severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients.

### **Immune**

#### *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 Bio-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, Bio-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](#).

## **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**

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 [4.2 Recommended Dose and Dosage Adjustment](#).

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 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. The adverse reaction rates observed in the clinical trials; therefore, 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). There were a limited number of *H. pylori* positive patients in these studies and therefore, definitive conclusions with regard to long-term consequences of *H. pylori* infection and acid suppressive treatment on gastric inflammation in this sub-group cannot be made.

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

Preferred term	Number of patients	Percentage of patients
Headache	24	2.137
Diarrhea	18	1.603
Nausea	13	1.158

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  $\geq 1\%$  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  $\geq 1\%$ , 20 or 40 mg**

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

A total of 1217 patients were treated with triple combination therapy including pantoprazole sodium and two antibiotics. Adverse events noted at a frequency of greater than or equal to 1% when

pantoprazole sodium was used in combination with antibiotics for the eradication of an *H. pylori* infection included the following:

Regardless of the combination regimen, the most frequently reported events were gastrointestinal system disorders, followed by autonomic nervous system disorders and “body as a whole”, or generalized disorders.

### 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 are listed below by body system

Infections and Infestations	Sepsis
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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 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 portions of the [8 ADVERSE REACTIONS](#) section, the [10.3 Pharmacokinetics Special Populations and Conditions](#) section, and the [7 WARNINGS AND PRECAUTIONS Hepatic/Biliary/Pancreatic](#) section.

#### 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; Erythema multiforme; Toxic epidermal necrolysis (Lyell syndrome); Photosensitivity; DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) (some fatal); Alopecia; Acne; Exfoliative dermatitis

\* May be related to the occurrence of Hypomagnesemia

There have been post-marketing reports of 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
Antibiotics (amoxicillin, clarithromycin and metronidazole)	CT	No clinical effect	<p>See 7 <a href="#">WARNINGS AND PRECAUTIONS, Antibiotic Combination Therapy</a></p> <p>No pharmacokinetic interaction was observed between pantoprazole sodium and the following antibiotic combinations: metronidazole plus clarithromycin, metronidazole plus amoxicillin, amoxicillin plus clarithromycin.</p> <p>In single dose pharmacology studies, concomitant administration of pantoprazole with combinations of amoxicillin, clarithromycin, and/or metronidazole, in fasted healthy volunteers showed a lack of interaction. Antibiotic combination therapy was well tolerated, with no clinically relevant changes in vital signs, ECG, or clinical laboratory parameters. Equivalence between the test (i.e., in combination regimen) and the respective reference (i.e., subject medication) was concluded when the 90% CI was within the equivalence range of 0.67 to 1.5 for the <math>AUC_{0-\infty}</math> and <math>C_{max}</math>.</p> <p>The ratio of test/reference point estimates (90% CI), in concomitant administration of the following were:</p>

			<ul style="list-style-type: none"> <li>• pantoprazole (40 mg) with clarithromycin (500 mg) and metronidazole (500 mg) the AUC<sub>0-∞</sub> was 1.02 (0.99, 1.06), 1.16 (1.04, 1.28), 1.11 (0.98, 1.25) and C<sub>max</sub> was 1.08 (0.99, 1.14), 1.15 (0.91, 1.45), 1.21 (1.06, 1.39) for metronidazole, clarithromycin and pantoprazole, respectively.</li> <li>• pantoprazole (40 mg) with clarithromycin (500 mg) and amoxicillin (1000 mg) the AUC<sub>0-∞</sub> was 0.93 (0.85, 1.02), 1.14 (1, 1.31), 1.1 (1.03, 1.18) and C<sub>max</sub> was 0.97 (0.86, 1.1), 1.18 (1, 1.4), 1.11 (0.94, 1.31) for amoxicillin, clarithromycin and pantoprazole, respectively.</li> </ul> <p>In a preclinical study, pantoprazole sodium in combination therapy with various antibiotics (including tetracycline, clarithromycin, and amoxicillin) was shown to have a potentiating effect on the elimination rate of <i>Helicobacter pylori</i> infection. See <a href="#">15 MICROBIOLOGY</a>.</p>
Antacids	CT	No clinical effect	Concomitant use of antacids does not affect the pharmacokinetics of pantoprazole sodium.
Antiretroviral Drugs	T	↓rilpivirine, atazanavir, nelfinavir ↑saquinavir	<p>See <a href="#">7 WARNINGS AND PRECAUTIONS, Drug Interactions with Antiretroviral Drugs</a></p> <p><i>Rilpivirine</i>: Co-administration is contraindicated due to significant decreases in rilpivirine exposure and loss of therapeutic effect. See <a href="#">2 CONTRAINDICATIONS</a>.</p> <p><i>Atazanavir</i>: Co-administration of pantoprazole magnesium with atazanavir is not recommended.</p> <p>Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C<sub>max</sub> and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir. (see Atazanavir Product Monograph).</p>

			<p><i>Nelfinavir:</i> Co-administration of pantoprazole magnesium with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and C<sub>max</sub> for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively) (see Nelfinavir Product Monograph).</p> <p><i>Saquinavir:</i> 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 Saquinavir Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and C<sub>max</sub> by 75%.</p>
Methotrexate	C	-	<p>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 hydroxyl methotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.</p> <p>See <a href="#">7 WARNINGS AND PRECAUTIONS, General, Concomitant Use with Methotrexate</a></p>

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

### Cytochrome P 450 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 proton pump inhibitors, 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 Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Bio-PANTOPRAZOLE treatment should be stopped 14 days before CgA measurements. See [10.2 Pharmacodynamics, Pharmacodynamic Properties](#).

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Pantoprazole sodium 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 stomach.

Pantoprazole 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 (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.

Treatment with pantoprazole alone has a limited effect on infections of *Helicobacter pylori*, a bacterium implicated as a major pathogen in peptic ulcer disease. Approximately 90-100% of patients with duodenal ulcers, and 80% of patients with gastric ulcers, are *H. pylori* positive. Preclinical evidence suggests that there is a synergistic effect between pantoprazole sodium and selected antibiotics in eradicating *H. pylori*. In infected patients, eradication of the infection with pantoprazole sodium and appropriate antibiotic therapy leads to ulcer healing, accompanied by symptom relief and a decreased rate of ulcer recurrence.

In single dose clinical pharmacology studies, pantoprazole was administered concomitantly with combinations of amoxicillin, clarithromycin, and/or metronidazole. When a single dose of pantoprazole was administered to healthy volunteers in combination with metronidazole plus amoxicillin, with clarithromycin plus metronidazole, or with clarithromycin plus amoxicillin, lack of interaction between any of the medications was shown.

## 10.2 Pharmacodynamics

In clinical studies investigating intravenous (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 proton pump inhibitors 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 H<sub>2</sub>-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
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.

### ***Non-clinical Pharmacodynamics***

*In vivo*, pantoprazole produced marked and long-lasting inhibition of basal and stimulated gastric acid secretion with median effective dose (ED<sub>50</sub>) 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 anesthetized 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.

### 10.3 Pharmacokinetics

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

Dose (mg)	C <sub>max</sub> (mcg/mL)	t <sub>max</sub> (h)	t <sub>1/2</sub> (h)	AUC (mcg·h/mL)
40	2.5	2-3	1	5

Pantoprazole shows linear pharmacokinetics, i.e., AUC and C<sub>max</sub> 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<sub>max</sub> is approximately 2.5 mcg/mL with a t<sub>max</sub> of 2 to 3 hours. The AUC is approximately 5 mcg.h/mL. There is no food effect on AUC (bioavailability) and C<sub>max</sub>. 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).

For combination therapy of pantoprazole with clarithromycin and amoxicillin or metronidazole please refer to section [9.4 Drug-Drug Interactions](#).

#### **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%.

### ***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.

## **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

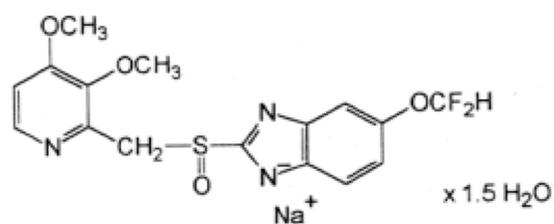
#### Drug Substance

Proper name: pantoprazole sodium

Chemical name: Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide Sesquihydrate

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

Structural formula:



Physicochemical properties:

Physical description: White to off-white powder

Solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, dilute acids, etc.): Pantoprazole sodium is freely soluble in ethanol and water, and practically insoluble in hexane.

pH: 1% aqueous solution: 10.05  
10% aqueous solution: 10.85

pKa: 3.94 pyridine;  
8.23 benzimidazole

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

**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

**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	Pantoprazole 20 mg QD or misoprostol 400 mcg (200	Total 515 Pantoprazole 257	31-93	Male (139) and female (376)

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
	comparison in patients 55 years or older with an underlying rheumatic disease that had to be continuously treated with least one NSAID	mcg BD), Oral, 6 months	Misoprostol 258		

**Table 11. Summary of patient demographics for clinical trials in *Helicobacter pylori* associated duodenal ulcer in adult patients**

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Triple combination therapy	Randomized, double-blind, multicenter, parallel group study	<p>Study 1 &amp; 2: Pantoprazole sodium 40 mg + clarithromycin 500 mg + metronidazole 500 mg, BID, Oral, 1 week</p> <p>Study 2, 3 &amp; 4: Pantoprazole sodium 40 mg + amoxicillin 1000 mg + clarithromycin 500 mg, BID, Oral, 1 week</p>	Study 1=213; Study 2=283; Study 3=62 and Study 4=57	20-95	Male and Female

**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

## 14.2 Study Results

### Symptomatic gastro-esophageal reflux disease

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 night time 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 night time 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.

### Prevention of gastrointestinal lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs)

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.

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.

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 below.

**Table 13. 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 od (P20) vs pantoprazole 40 mg od (P40) vs omeprazole 20 mg od (O20)			Study 2; Pantoprazole 20 mg od (P20) vs misoprostol 200 mcg 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 M200
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	98	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, treatment with pantoprazole 20 mg od was equivalent to the treatment with pantoprazole 40 mg od and omeprazole 20 mg od in this indication.

In a second six-month study involving 515 patients requiring continuous intake of NSAIDs, 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.

### ***Helicobacter pylori* associated duodenal ulcer**

**Table 14. Results of studies in patients with active duodenal ulcer who were *H. pylori* positive**

Treatment		Eradication Rate (ITT + kpa analysis)	95% CI	Ulcer Healing Rate after therapy cessation (MITT analysis)	95% CI
Pantoprazole 40 mg + clarithromycin 500 mg + metronidazole 500 mg, all twice daily for 1 week (PCM)	Study 1	83%	75-90%	88%	80-93%
	Study 2	96%	91-98%	Not assessed	
Pantoprazole 40 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for 1 week (PAC)	Study 2	93%	88-97%	Not assessed	
	Study 3	86%	68-96%	88%	72-97%
	Study 4	86%	74-94%	92%	82-97%

ITT + kpa: Patients who were *H. pylori* positive at the initial examination and had complete and valid results for the requisite (based on the study) number of tests at the appropriate follow-up visit. In study 1, 3 of 4 *H. pylori* tests must be complete and valid.;

Study 1: Patients with active duodenal ulcer, were assessed for *H. pylori* status by UBT, histology, culture and rapid urease, n=213 (ITT + kpa);

Study 2: Patients with active duodenal ulcer, were assessed for *H. pylori* status by UBT and rapid urease pre-treatment and by UBT post-treatment, n=283 (ITT + kpa)

Study 3: Patients with active duodenal ulcer, were assessed for *H. pylori* status by rapid urease and UBT pre-treatment and by UBT and histology post-treatment, n=62 (ITT + kpa);

Study 4: Patients with active duodenal ulcer, were assessed for *H. pylori* status by rapid urease, culture and histology pre-treatment and culture and histology post-treatment, n=57 (ITT + kpa)

### **Prevention of Relapse of Reflux Esophagitis**

The long-term maintenance of healing of erosive esophagitis was assessed in two U.S. randomised, double-blind, parallel-group, active controlled studies. Eligible patients in both studies had a recent history of grade II or III (Hetzel-Dent) erosive esophagitis, and endoscopically demonstrated healing. Both studies used as the primary endpoint endoscopically demonstrated recurrence (assessed at month 1, 3, 6 and 12) of erosive esophagitis ('relapse'). Gelusil antacid tablets were to be taken as needed for symptomatic relief after 5 or more minutes of retrosternal pain, acid regurgitation, or dysphagia, but not within 1 hour before or after taking study medication. Ad hoc endoscopies were

performed when symptoms of GERD occurred for more than 3 consecutive days. As the primary analysis Kaplan Meier's method was performed, whereas the discrete analysis was secondary. In the U.S. studies, there were a limited number of *H. pylori* positive patients. Results for this sub-group are therefore qualitative only.

In the US studies, the results of Kaplan-Meier's analyses showed that the cumulative proportion of relapse over time was dose-related for the pantoprazole treatment groups. The cumulative proportion of relapse at 12 months for patients treated with pantoprazole 20 mg and pantoprazole 40 mg exhibited a statistically significant difference in the pooled data (p-value=0.001) and in the data of one of the studies (3001A1-302-US: p-value =0.012, 3001A1- 303-US p-value=0.052) (p-values adjusted for pairwise comparison).

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

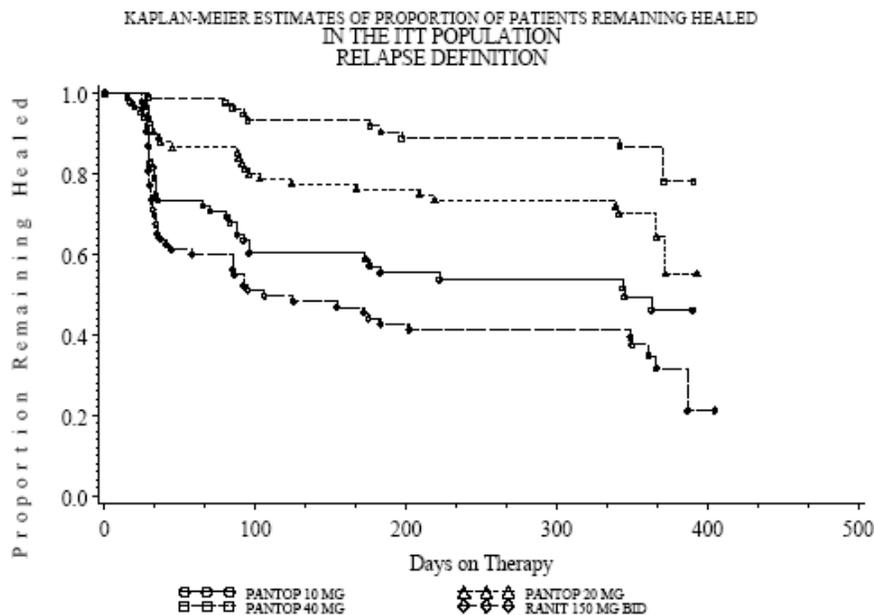
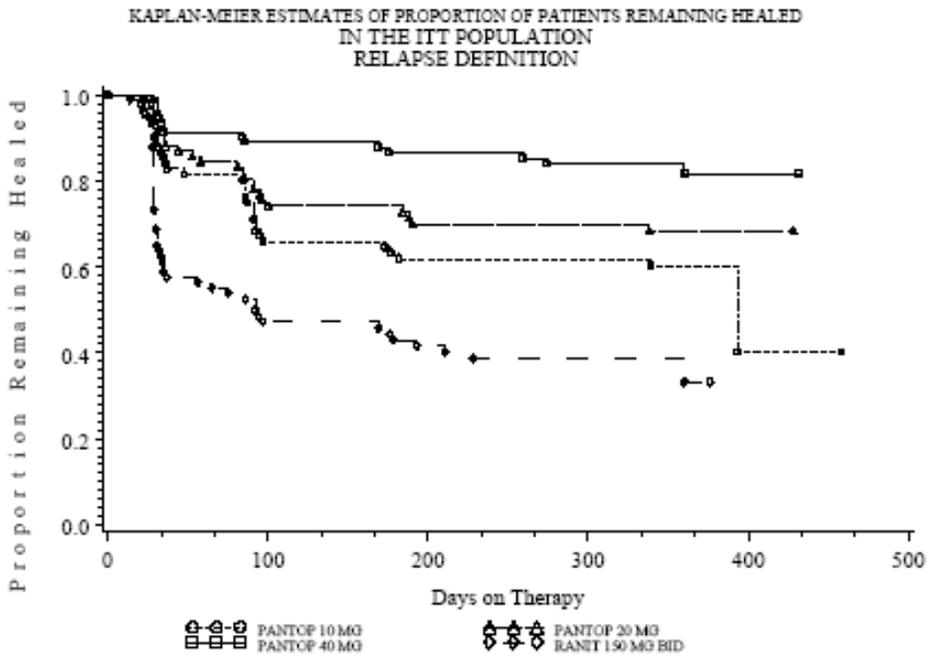


Figure 2 - Kaplan-Meier plot; 3001A1-303-US



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).

**Table 15. 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(%)
<b>Study 3001A1-302-US</b>			
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)
Month 12	25/75 (33.3)*	10/64 (15.6)* <sup>a</sup>	52/76(68.4)
<b>Study 3001A1-303-US</b>			
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)*	12/85 (14.1)*	51/79(64.6)
Month 12	25/73 (34.2)*	15/78 (19.2)*	52/78(66.7)
<b>Pooled data</b>			
Month 12	50/148 (33.8) *	25/142 (17.6) * <sup>a</sup>	104/154 (67.5)

\*Statistically significant between treatment and ranitidine at 0.05 level; <sup>a</sup> Statistically significant between pantoprazole 40 mg and 20 mg with adjusted p-value (Holm procedure). Mean age 302-US 49.2 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, US-302: 85% *H. pylori* negative, 15% *H. pylori* positive, US-303: 88% *H. pylori* negative, 12% *H. pylori* positive.

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 16. 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, at that time determination of *H. pylori* status and eradication of *H. pylori* was not widely introduced.

### 14.3 Comparative Bioavailability Studies

A double blinded, randomized, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Bio-PANTOPRAZOLE (Pantoprazole sodium) 40mg enteric-coated tablets (Biomed Pharma) with <sup>Pr</sup>PANTOLOC® (Pantoprazole sodium) enteric-coated tablets (Nycomed Canada Inc.) in 64 Asian normal, healthy, adult, male and female human subjects under fasting conditions was conducted and the results from 61 subjects are summarized in the following table.

<b>Pantoprazole (1 x 40 mg)</b> From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
AUC <sub>0-t</sub> (ng*hr/mL)	10690.25 14124.1 (78.7)	10084.6 13059.39 (77.58)	106.19	98.37 -114.64
AUC <sub>0-inf</sub> (ng*hr/mL)	11270.93 15796.13 (88.98)	10570.9 14447.07 (88.62)	106.87	98.39 -116.08
C <sub>max</sub> (ng/mL)	3444.3 3600.38 (27.94)	3341.01 3463.91 (24.86)	103.44	96.88-110.43
T <sub>max</sub> <sup>§</sup> (h)	3.15 (32.07)	2.86 (35.68)		
T <sub>1/2</sub> <sup>€</sup> (h)	3.5 (89.09)	3.21 (30.96)		

\* Bio-PANTOPRAZOLE (pantoprazole sodium), 40mg enteric-coated tablets (Biomed Pharma)

† Pantoloc® (pantoprazole sodium) 40mg enteric-coated tablets (Nycomed Canada Inc) were purchased in Canada.

§ Expressed as arithmetic mean (CV %) only

€ Expressed as the arithmetic mean (CV%) only

## 15 MICROBIOLOGY

### *In vivo* Studies

Female mice were infected with *Helicobacter felis* on Days 1, 3, and 5 by gavage with 10<sup>8</sup> - 10<sup>9</sup> bacteria per animal. Starting on Day 8, the mice were treated three times daily with placebo or active drug (pantoprazole and/or amoxicillin, clarithromycin, tetracycline) for four days. One day after the last treatment, the mice were sacrificed and a biopsy of the antrum was subjected to a urease test, with only those tests showing a dark violet colour considered to contain urease-positive *Helicobacter*.

**Table 17. Doses of the active agents, the number of infected animals per group, and resulting elimination rates for the *H. felis* infection**

Active Dosing Groups	Elimination Rates
Pantoprazole 100 mg/kg tid (n=10)	0%
Amoxicillin 0.5 mg/kg tid (n=10)	40%
Amoxicillin 3.0 mg/kg tid (n=10)	100%
Clarithromycin 0.5 mg/kg tid (n=10)	10%
Clarithromycin 3.0 mg/kg tid (n=10)	70%
Tetracycline 3.0 mg/kg tid (n=20)	55%
Tetracycline 15.0 mg/kg tid (n=10)	90%
Pantoprazole 100 mg/kg tid + amoxicillin 0.5 mg/kg tid (n=10)	100%
Pantoprazole 100 mg/kg tid + clarithromycin 0.5 mg/kg tid (n=10)	90%
Pantoprazole 100 mg/kg tid + tetracycline 3.0 mg/kg tid (n=20)	80%

In the infected, placebo dosed positive control group, 24 of the 25 mice had positive urease tests, while the negative control group (not infected, placebo dosed) all had negative urease tests.

Pantoprazole alone was without effect on *Helicobacter pylori* infection, while in combination therapy with the antibiotics, pantoprazole had a potentiating effect on the elimination rate of *Helicobacter pylori* infection. The results show a potentiation by a factor of about six, i.e., pantoprazole plus the low dose antibiotic achieved an infection elimination rate greater than or approximately equal to the higher dose of antibiotic given alone, which was dosed at five to six times higher than the low dose.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology:

#### Acute Toxicity

In acute toxicity studies in mice the mean lethal dose (LD<sub>50</sub>) 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 > 1000 mg/kg

for oral administration.

Acute toxicity studies were conducted on B8810-044, the major degradation product of pantoprazole. The approximate LD<sub>50</sub> 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 intravenous 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 18. Acute toxicity studies of Pantoprazole**

Species	Sex	Route	ca. LD <sub>50</sub> * (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 gelatin 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. Hypergastrinemia 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.

In a four week oral toxicity study, Beagle dogs were given daily oral doses of encapsulated commercial products including pantoprazole, clarithromycin, metronidazole, and amoxicillin. Groups of three male

and three female dogs received the following daily doses of pantoprazole and/or antibiotics:

Group 1 - pantoprazole 16 mg/kg

Group 2 - clarithromycin 75 mg/kg + metronidazole 50 mg/kg

Group 3 - pantoprazole 16 mg/kg + amoxicillin 120 mg/kg + metronidazole 50 m/kg

Group 4 - pantoprazole 16 mg/kg + amoxicillin 120 mg/kg + clarithromycin 50 mg/kg

Group 5 - pantoprazole 16 mg/kg + clarithromycin 75 mg/kg + metronidazole 50 mg/kg

Histomorphological investigations indicated that treatment with clarithromycin and metronidazole alone (Group 2) induced an atrophic gastritis, which was not seen when these products were given concomitantly with pantoprazole. In Group 5, however, the total mucosal appearance was diagnosed as quite normal, and the height of the mucosa was not decreased. In the recovery dogs, the mucosae were also judged to be normal.

In all groups dosed with clarithromycin (Groups 2, 4, 5), inflammation and hyperplasia of the gallbladder, together with degeneration of the renal papilla were noted. These changes were absent from the Group 5 recovery dogs (only tubular swelling, increased tubular pigment noted), indicating reversibility. A slight centrilobular hypertrophy was observed in the liver of most animals.

In dogs which had positive <sup>13</sup>C-urea breath tests prior to treatment, the Helicobacter-like organism responsible was eliminated in Groups 2 through 5, and remained eradicated in the Group 5 recovery animals.

Based on the results of this study, it was concluded that no additional toxic effects were observed during concomitant administration of different antibiotics with pantoprazole.

#### **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 pediatric 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.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1. PrPANTOLOC® (Enteric-Coated Tablets, 20 mg and 40 mg), submission control number: 255072, Product Monograph, Takeda Canada Inc. (April 01, 2022).

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### Pr **Bio-PANTOPRAZOLE**

#### **Pantoprazole Sodium Delayed-Release Tablets**

Read this carefully before you start taking **Bio-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 **Bio-PANTOPRAZOLE**.

#### **What is Bio-PANTOPRAZOLE used for?**

Bio-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.
- **Duodenal ulcer caused by the bacteria *Helicobacter pylori* (*H. pylori*).**  
Bio-PANTOPRAZOLE is used in combination with two antibiotics.
- **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 Bio-PANTOPRAZOLE work?**

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

#### **What are the ingredients in Bio-PANTOPRAZOLE?**

Medicinal ingredients: pantoprazole sodium sesquihydrate.

Non-medicinal ingredients: Calcium stearate, colloidal silicon dioxide, crospovidone, mannitol, hydroxypropylmethyl cellulose, polyethylene glycol, sodium carbonate anhydrous, sodium starch glycollate, sodium hydroxide, Eudragit (contains: methacrylic acid-ethyl acrylate copolymer, Sodium lauryl sulfate and polysorbate), opadry yellow contains: lecithin (soy), titanium dioxide, yellow iron oxide, polyvinyl alcohol, talc and xanthan gum).

Composition of printing ink: Shellac, isopropyl alcohol, black iron oxide, n-butyl alcohol, propylene glycol and ammonium hydroxide.

**Bio-PANTOPRAZOLE comes in the following dosage forms:**

- Delayed-Release Tablet, 20 mg and 40 mg.

**Do not use Bio-PANTOPRAZOLE if:**

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

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

- are taking other medications (see **The following may interact with Bio-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 healthcare professional.
- suffer these effects:
  - unexplained weight loss
  - severe or persistent diarrhea
  - repeated vomiting
  - vomiting blood
  - dark stools
  - tiredness (anemia)
  - difficulty in swallowing.
  - 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:**

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

Depending on your condition, your healthcare professional 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 healthcare professional 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 healthcare professional.

Using Bio-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 with Bio-PANTOPRAZOLE:**

- Warfarine
- Atazanavir
- Méthotrexate
- Itraconazole
- Erlotinib
- Nelfinavir
- Saquinavir/ritonavir
- Kétoconazole
- Posaconazole

**How to take Bio-PANTOPRAZOLE:**

- Take Bio-PANTOPRAZOLE in the morning.
  - with or without food
- Swallow the tablet(s) whole with water.
- Do not crush or chew the tablet(s).

**Usual adult dose:**

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

Bio-PANTOPRAZOLE may be used in combination with two antibiotics to treat ulcers caused by *H. pylori*. Bio-PANTOPRAZOLE and both antibiotics are to be taken twice a day, or as prescribed by your healthcare professional.

**Overdose:**

If you think you, or a person you are caring for, have taken too much Bio-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 Bio-PANTOPRAZOLE?**

Like all medicines, Bio-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 Bio-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 healthcare professional 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.

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>RARE</b>			
Disturbances in vision. Most cases reported are not serious.			✓
<b>UNKNOWN</b>			
Liver damage. Symptoms include a yellow tinge to the skin and eyes.			✓
Serious skin reactions. Symptoms include widespread rash, itching, or hives. Peeling of the skin, blisters on the skin, mouth, nose, eyes and genitals are other symptoms.			✓
Muscle wasting.			✓
<i>Clostridium difficile</i> colitis (bowel inflammation). Symptoms include severe (watery or bloody) diarrhea, fever, and abdominal pain or tenderness.			✓

<p>Microscopic colitis (inflammation of the gut) symptoms include chronic watery diarrhea, abdominal pain, cramps or bloating, weight loss, nausea, uncontrollable bowel movement.</p> <p>Signs of dehydration such as extreme thirst, Less frequent urination, dark-coloured urine, fatigue, dizziness, confusion.</p> <p>The symptoms of microscopic colitis can come and go frequently. If you have watery diarrhea that lasts more than a few days, contact your healthcare professional</p>	✓		
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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 Bio-PANTOPRAZOLE at room temperature, 15°C- 30°C.

Keep out of reach and sight of children.

#### **If you want more information about Bio-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](#)); or by contacting the sponsor:

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This leaflet was prepared by Biomed Pharma.

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