PRODUCT MONOGRAPH

^{Pr}VAN-Pantoprazole

Pantoprazole Sodium Delayed-Release Tablets, Manufacturer's Standard

40 mg pantoprazole (as pantoprazole sodium sesquihydrate)

H^+, K^+- ATPase Inhibitor

Manufacturer and Distributor:
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PrVAN-Pantoprazole

Pantoprazole sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Delayed-Release Tablet 40 mg pantoprazole	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

Note: As with all proton pump inhibitors, when VAN-Pantoprazole (pantoprazole sodium) 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.

INDICATIONS AND CLINICAL USE

VAN-Pantoprazole (pantoprazole sodium) 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*

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, 40 mg pantoprazole once daily have been used for 3 years in controlled clinical trials.

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 PHARMACOLOGY.

Pediatrics:
The safety and effectiveness of pantoprazole in children have not yet been established.

CONTRAINDICATIONS

Patients who are hypersensitive to pantoprazole, substituted benzimidazole or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia, or melaena) and when gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with pantoprazole sodium 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.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see DRUG INTERACTIONS). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

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

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.

Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses,

and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

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.

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 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.

Hepatic/Biliary/Pancreatic& Renal

The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg pantoprazole. See ACTION & CLINICAL PHARMACOLOGY, Special Populations & Conditions.

The daily dose used in renal insufficient patients, as a rule, should not exceed the recommended dosage regimens. See ACTION & CLINICAL PHARMACOLOGY, Special Populations & 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.

Endocrine and Metabolism

Hypomagnesaemia

Hypomagnesaemia, 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. In most patients, treatment of hypomagnesaemia 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 hypomagnesaemia (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 hypomagnesaemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Special Populations

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 REPRODUCTION and TERATOLOGY.

Nursing Women:
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.

Pediatrics:
The safety and effectiveness of pantoprazole in children have not yet been established.

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 PHARMACOLOGY. 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 DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

ADVERSE REACTIONS

Adverse Drug 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%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 (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.

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

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

Adverse drug reactions with a frequency of 0.1 to 1% related to 40 mg pantoprazole

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: Hypertriglyceridaemia

Metabolic and Nutritional: 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 have been reported in individuals receiving pantoprazole therapy with 40 mg once daily in short-term clinical trials (duration of up to 3 months).

Adverse drug reactions with a frequency of 0.1 to 1% related to pantoprazole, 40 mg

Gastrointestinal Disorders: Diarrhea, Flatulence, Nausea, Constipation, Abdominal Pain

Nervous System Disorders: Headache, Dizziness

Skin and Subcutaneous Tissue Disorders: Pruritus

In addition, the following adverse events considered unrelated, or unlikely related by the investigator have been reported in individuals receiving pantoprazole therapy with 40 mg once daily in short-term and long-term clinical trials.

Adverse Events with a frequency of > 1 %, 40 mg
Influenza Like Illness, Headache, Diarrhea

Adverse Events with a frequency of 0.1 to 1%, 40 mg

Bronchitis, Nausea, Back Pain, Abdominal Pain Upper, Upper Respiratory Tract Infection, Non-accidental Injury, Sinusitis, Abdominal Pain, Dizziness, Arthralgia, Vomiting, Pharyngitis, Chest Pain, Gastroenteritis, Dyspepsia, Urinary Tract Infection, Eructation, Pyrexia, Cough, Depression, Hypertension, Pain in Limb, Constipation, Fatigue, Operation, Neck Pain, Nasopharyngitis, Alanine Aminotransferase Increased, Hemorrhoids, Pain, Flatulence, Viral Infection, Hypertriglyceridaemia, Toothache, Hypersensitivity, Rash, Abdominal Pain Lower, Pneumonia, Abdominal Distension, Dyspnoea, Muscle Cramp, Rhinitis, Peripheral Edema, Tonsillitis, Angina Pectoris, Cholelithiasis, Sinus Congestion, Influenza, Vertigo, Insomnia, Infection, Osteoarthritis, Hypercholesterolaemia, Pruritis, Eczema, Sleep Disorder, Migraine, Aspartate Aminotransferase Increased, Hyperglycemia, Musculoskeletal Discomfort, Blood Triglycerides Increased, Myocardial Infarction, Tendonitis, Weight Increased, Rectal Hemorrhage, Cystitis, Nasal Congestion, Arthritis, Contusion, Abdominal Discomfort, Enteritis

The following Serious Adverse Events regardless of causality were reported with a frequency of <0.1%, 40 mg:
Sepsis

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:

In combination with clarithromycin and metronidazole (n=725):

Body as a Whole: headache (1.8%), tiredness (1.1%)

Central and Peripheral Nervous System: dizziness (1.4%)

Gastrointestinal: diarrhea (4.8%), nausea (3.7%), upper abdominal pain (1.9%), tongue pain (1.2%), loose stools (1.0%), buccal inflammation (1.0%)

Hepatobiliary: hepatic enzymes increased (1.2%)

Special Senses: bitter taste (4.0%), metallic taste (2.1%)

In combination with amoxicillin and clarithromycin (n=492):

Body as a Whole: headache (1.8%), pain (1.0%)

Skin and Appendages: exanthema (1.2%)

Gastrointestinal: diarrhea (10.0%), bitter taste (3.0%), upper abdominal pain (1.4%), nausea (1.2%)

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.

Abnormal Hematological & Clinical Chemistry Findings

Please refer to the Hepatobiliary Disorders and the Laboratory Parameters portions of the ADVERSE REACTION section, the ACTION & CLINICAL PHARMACOLOGY Special Populations & Conditions section, and the WARNINGS & PRECAUTIONS Hepatic/Biliary/Pancreatic section.

Post-Market Adverse Drug 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:

Interstitial nephritis; Stevens-Johnson Syndrome; Erythema multiforme; Toxic epidermal necrolysis (Lyell syndrome); Photosensitivity; Hyponatraemia; Hypomagnesaemia, Hepatocellular injury; Jaundice; Hepatocellular failure; Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in the case of pre-existence). Hypokinesia, Anterior ischemic optic neuropathy; Pancreatitis; Increased salivation; Speech disorder; Elevated creatine phosphokinase; Rhabdomyolysis; Alopecia; Acne; Exfoliative dermatitis; Nervousness; Tremor; Tinnitus; Paresthesia; Photophobia; Vertigo; Increased appetite; Hematuria; Impotence; Eosinophilia; Osteoporosis and osteoporosis-related fractures.

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

Uncommon: Headache; Dizziness; Nausea/vomiting; Abdominal distension and bloating; constipation; dry mouth; Abdominal pain and discomfort; Rash/exanthema/eruption; Pruritus; Asthenia, fatigue and malaise; Liver enzymes increased (transaminases, γ-GT); Sleep disorders.

Rare: Agranulocytosis; Disturbances in vision/blurred vision; Urticaria; Angioedema; Myalgia; Arthralgia; Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes; Body temperature increased; Oedema peripheral; Gynaecomastia; Hypersensitivity (including anaphylactic reactions and anaphylactic shock); Bilirubin increased; Depression (and all aggravations); Taste Disorder.

Very rare: Thrombocytopenia; Leukopenia; Pancytopenia; Disorientation (and all aggravations).

Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

DRUG INTERACTIONS

Overview

Pantoprazole undergoes extensive hepatic metabolism via cytochrome P450-mediated oxidation. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways which include oxidation by CYP3A4. 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).

Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton pump inhibitors might result in a substantial reduction in the bioavailability of these

HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see WARNINGS AND PRECAUTIONS).

Drug-Drug 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. Concomitant use of antacids does not affect the pharmacokinetics of pantoprazole sodium.

Clinical studies have shown that there is no pharmacokinetic interaction between pantoprazole and the following antibiotic combinations: metronidazole plus clarithromycin, metronidazole plus amoxicillin, amoxicillin plus clarithromycin.

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 *Helicobacter pylori* infection. (See MICROBIOLOGY)

Although no interaction during concomitant administration of warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/ INR is recommended after initiation, termination or during irregular use of pantoprazole.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Drug-Food Interactions

Consumption of food does not affect the pharmacokinetics (AUC and Cmax) of pantoprazole sodium. See HUMAN PHARMACOLOGY.

Drug-Laboratory 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.

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.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

DUODENAL ULCER
The recommended adult dose of VAN-Pantoprazole (pantoprazole sodium) 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 VAN-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 VAN-Pantoprazole 40 mg together with clarithromycin 500 mg and amoxicillin 1000 mg, all twice daily.

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.

40 mg once daily has been demonstrated to be effective in the maintenance of healing of reflux esophagitis.

PREVENTION OF GASTROINTESTINAL LESIONS INDUCED BY NSAIDs
The recommended adult oral dose of pantoprazole is 20 mg, given once daily in the morning.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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.

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.

Reconstitution:
Not applicable.

OVERDOSAGE

For management of a suspected drug overdose contact your regional Poison Control Centre immediately.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
VAN-Pantoprazole (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 sodium is a substituted benzimidazole that accumulates in the acidic environment of the parietal cells after absorption. Pantoprazole sodium is then converted into the active form, acyclic sulphenamide, which binds to the H^+, K^+-ATPase, thus inhibiting both the basal and stimulated gastric acid secretion. Pantoprazole sodium 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.

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.

Pharmacokinetics

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, Cmax is approximately 2.5 µg/mL with a t_{max} of 2 to 3 hours. The AUC is approximately 5 µg.h/mL. There is no food effect on AUC (bioavailability) and Cmax.

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.

Excretion: 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).

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

life, clearance and volume of distribution are considered to be dose-independent. Following repeated i.v. or oral administration, the AUC of pantoprazole was similar to a single dose.

Special Populations and Conditions

Pediatrics:

The safety and effectiveness of pantoprazole in children have not yet been established.

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. 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%.

STORAGE AND STABILITY

Store at 15 ºC to 30 ºC in the recommended packaging.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VAN-Pantoprazole (pantoprazole sodium) is available as enteric-coated tablets for oral administration.

VAN-Pantoprazole 40 mg tablets are yellow, oval; biconvex enteric coated tablets plain on both sides and contain 40 mg pantoprazole (45.1 mg pantoprazole sodium sesquihydrate).

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

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) and opadry yellow (contains: lecithin (soy), titanium dioxide, yellow iron oxide, polyvinyl alcohol, talc and xanthan gum).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

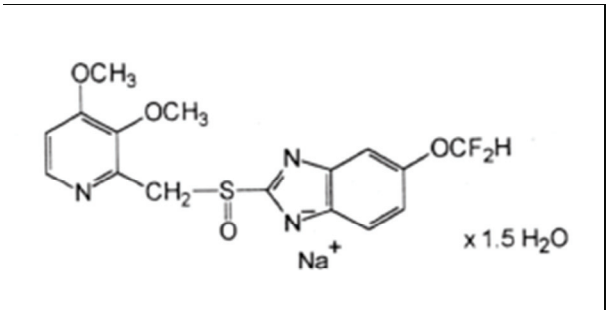
Drug Substance

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: $C_{16}\ H_{14}\ F_2\ N_3\ NaO_4\ S \times 1.5\ H_2\ O$ M_r: 432.4

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

CLINICAL TRIALS

Comparative Bioavailability Studies:

A double blinded, randomized, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of VAN-Pantoprazole (Pantoprazole sodium) 40mg enteric-coated tablets (Vanc Pharmaceuticals Inc) with [Pr]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.

Pantoprazole **(1 x 40 mg)** From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-t} (ng*hr/mL)	10690.25 14124.10 (78.7)	10084.60 13059.39 (77.58)	106.19	98.37 -114.64
AUC_{0-inf} (ng*hr/mL)	11270.93 15796.13 (88.98)	10570.90 14447.07 (88.62)	106.87	98.39 -116.08
C_{max} (ng/mL)	3444.30 3600.38 (27.94)	3341.01 3463.91 (24.86)	103.44	96.88-110.43
T_{max}§ (h)	3.15 (32.07)	2.86 (35.68)		
$T_{½}$€ (h)	3.50 (89.09)	3.21 (30.96)		

* VAN-Pantoprazole (pantoprazole sodium), 40mg enteric-coated tablets (Vanc Pharmaceuticals Inc)
† 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

A double blinded, randomized, two-sequence, two-treatment, three-period, semi-replicate crossover, single dose, bioequivalence study of VAN-Pantoprazole (pantoprazole sodium) enteric coated 40mg tablets (Vanc Pharmaceuticals Inc.) with [Pr]PANTOLOC® (pantoprazole sodium) 40mg enteric-coated tablets (Nycomed Canada Inc.) in 48 Asian normal, healthy, adult, male and female human subjects under fed conditions was conducted and the results from 42 subjects are summarized in the following table.

Pantoprazole **(1 x 40 mg)** From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-t} (ng*hr/mL)	7319.83 13781.51 (101.33)	7503.37 11004.15 (106.18)	97.55	89.86 -105.90
AUC_{0-inf} (ng*hr/mL)	7506.41 14284.33 (102.80)	7693.19 11424.40 (107.14)	97.57	90.86 – 104.78
C_{max} (ng/mL)	2397.98 2750.74 (43.47)	2498.94 2719.83 (37.76)	95.96	84.48-109.00
T_{max}§ (h)	7.50 (2.00-20.00)	6.00 (2.50-20.00)		
$T_{½}$€ (h)	3.82 (93.05)	2.96 (104.65)		

* VAN-Pantoprazole (pantoprazole sodium), 40mg enteric-coated tablets (Vanc Pharmaceuticals Inc.)
† Pantoloc® (pantoprazole sodium) 40mg enteric-coated tablets (Nycomed Canada Inc) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

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 nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking pantoprazole sodium consumed significantly fewer antacid tablets per day than those taking placebo.

In a second US study involving 215 patients, a significantly greater proportion of the patients in the pantoprazole sodium treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking pantoprazole sodium consumed significantly fewer antacid tablets per day than those taking nizatidine.

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.

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 µg bid (M200)		
		Remission Rate (%)			Remission Rate (%)		
		P20 n = 196	P40 n = 199	O20 n = 200	P20 n = 257	M200 n = 258	p value P20 vs 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	96.0	98.0	95.3	0.16
	0-6	91.4	95.3	93.3	94.7	85.7	**0.005**
Symptomatic failure	0-3	98.8	100	98.8	98.5	92.3	**0.004**
	0-6	98.1	100	98.1	98.5	91.7	**0.002**

"In remission" is defined as patients who did not have any of the findings (e.g. "therapeutic failure", "endoscopic failure", or symptomatic failure" after 6 months).
Remission rates were obtained by subtracting failures from 100%.

In a six-month study involving 595 patients requiring continuous intake of NSAIDs, 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

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-

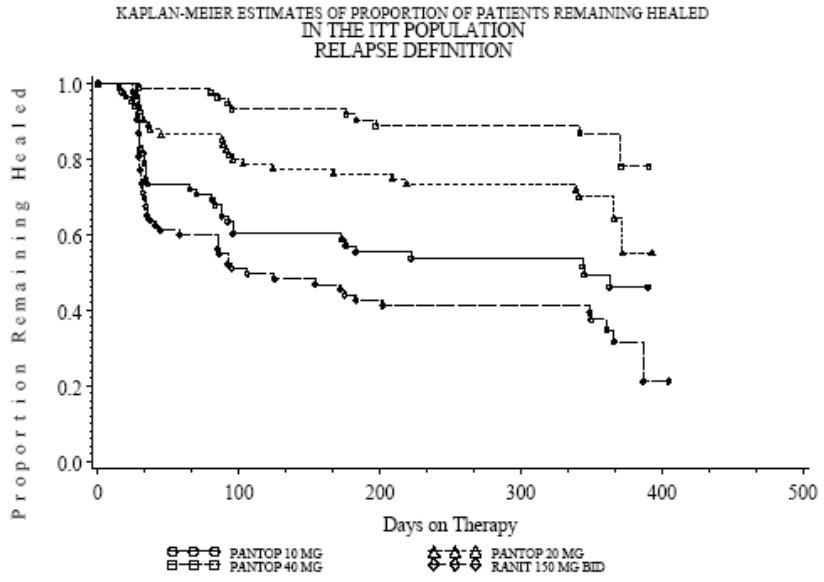
treatment and by UBT post-treatment, n=283 (ITT + kpa)
Study 3: Patients with active duodenal ulcer, were assessed for *H. pylori* status by rapid urease and UBT pre-treatment and by UBT and histology post-treatment, n=62 (ITT + kpa)
Study 4: Patients with active duodenal ulcer, were assessed for *H. 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

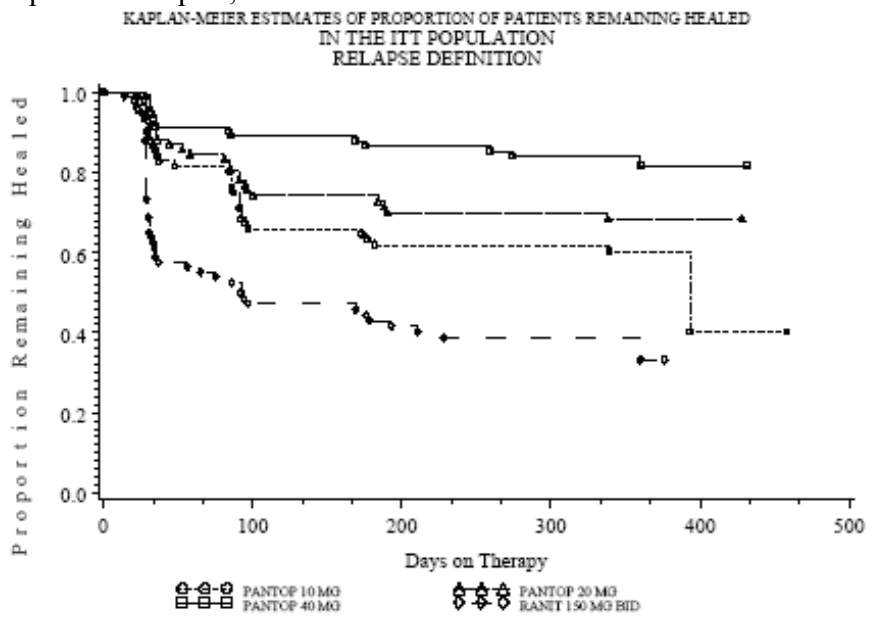
The long-term maintenance of healing of erosive esophagitis was assessed in two U.S. randomised, double-blind, parallel-group, active controlled studies. Eligible patients in both studies had a recent history of grade II or III (Hetzel-Dent) erosive esophagitis, and endoscopically demonstrated healing. 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. A*d 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).

Kaplan-Meier plot; 3001A1-302-US



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).

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

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

*Statistically significant between treatment and ranitidine at 0.05 level; [a]Statistically significant between pantorazole 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.

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.

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacodynamics:

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

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

In a battery of standard high-dose pharmacology tests, no influence of pantoprazole was detected on the central and peripheral nervous system. In conscious dogs as well as anaesthetized cats receiving single i.v. doses up to 10 mg/kg pantoprazole, no consistent changes with respect to respiratory rate, ECG, EEG, blood pressure and heart rate were observed. Higher doses led to modest and transient reductions in blood pressure and variable changes in heart rate. No influence

of pantoprazole was found on renal function and on autonomic functions, such as pancreatic and bile secretion, gastrointestinal motility and body temperature.

No consistent changes in the effects of ethanol, pentobarbitone, or hexobarbitone were induced by pantoprazole; only doses over 300 mg/kg prolonged the effects of diazepam.

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 Excretion
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.

HUMAN PHARMACOLOGY

Pharmacodynamics:
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 1: 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%

Dose	Mean %Inhibition of PSAO
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_2-blocker therapy (300 mg ranitidine at night) with regard to median 24-hour and daytime pH; however, not for nighttime measurements.

Table 2: 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 (Day Time)	1.8	4.4*	2.0
22.00-08.00 (Night Time)	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 3: 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.

Pharmacokinetics:
The absolute bioavailability of the pantoprazole tablet is 77%. Maximum serum concentrations of pantoprazole are reached within approximately 2.5 hours after oral intake. Following a dose of 40 mg, mean maximum serum concentrations of approximately 2 µg/mL and 3 µg/mL are reached after 2 to 3 hours. There is no food effect on AUC (bioavailability) and C_{max}. However, time to reach maximum serum concentrations is slightly increased when the drug is given together with a high caloric breakfast. Taking into account the long duration of action of pantoprazole, which by far exceeds the time period over which serum concentrations are measurable, this observed variation in t_{max} is considered to be of no clinical importance.

Pantoprazole is approximately 98% bound to serum protein.

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.

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.

Pantoprazole undergoes metabolic transformation in the liver. Approximately 82% of the oral dose is removed by renal excretion, and the remainder via feces. 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.

In single dose clinical pharmacology studies, pantoprazole was administered to fasting healthy volunteers concomitantly with combinations of amoxicillin, clarithromycin, and/or metronidazole. Pharmacokinetic characteristics of each of the subject medications administered alone were also evaluated as a reference point. Equivalence between the test (i.e., in combination regimen) and the respective reference was concluded when the 90% confidence interval was within the equivalence range of 0.67 to 1.50 for the $AUC_{0-\infty}$ and C_{max}.

The potential influence of the concomitant administration of pantoprazole 40 mg with clarithromycin 500 mg and metronidazole 500 mg on pharmacokinetic characteristics was evaluated following a single oral dose administered to fasted healthy volunteers. A lack of interaction was shown for each of the drugs (see Table 4 below).

Table 4: Point estimates and 90% CIs for the respective ratios of Test/Ref*

	Metronidazole	Clarithromycin	Pantoprazole
$AUC_{0-\infty}$	1.02 (0.99, 1.06)	1.16 (1.04, 1.28)	1.11 (0.98, 1.25)
C_{max}	1.08 (0.99, 1.14)	1.15 (0.91, 1.45)	1.21 (1.06, 1.39)

* Ref = drug alone
Test = combination

Concomitant administration was well tolerated, with no clinically relevant changes in vital signs, ECG, or clinical laboratory parameters noted.

The potential influence of the concomitant administration of pantoprazole 40 mg with clarithromycin 500 mg and amoxicillin 1000 mg on pharmacokinetic characteristics was also evaluated following a single oral dose administered to fasted healthy volunteers. A lack of interaction was shown for each of the drugs (see Table 5 below).

Table 5: Point estimates and 90% CIs for the respective ratios of Test/Ref*

	Amoxicillin	Clarithromycin	Pantoprazole
$AUC_{0-\infty}$	0.93 (0.85, 1.02)	1.14 (1.00, 1.31)	1.10 (1.03, 1.18)
C_{max}	0.97 (0.86, 1.10)	1.18 (1.00, 1.40)	1.11 (0.94, 1.31)

* Ref = drug alone
Test = combination

Concomitant administration was well tolerated, with no clinically relevant changes in vital signs, ECG, or clinical laboratory parameters noted.

MICROBIOLOGY

In vivo Studies

Female mice were infected with *Helicobacter felis* on Days 1, 3, and 5 by gavage with 10^8 - 10^9 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.

Doses of the active agents, the number of infected animals per group, and resulting elimination rates for the H. felis infection were as follows:

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.

TOXICOLOGY

ACUTE TOXICITY

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

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

Acute toxicity studies were conducted on B8810-044, the major degradation product of pantoprazole. The approximate LD_{50} values for mice (119-167 mg/kg) and rats (73-82 mg/kg) were lower than those for pantoprazole itself, after intravenous injection, but the toxic symptoms were similar to those noted for the drug. A 4-week repeat dose study was also conducted using this degradation product using the 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 6: Acute toxicity studies of Pantoprazole

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

* Doses refer to the sodium salt administered in solution

** sodium salt as dry powder in gelatine capsules

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

CHRONIC TOXICITY

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

and 30 mg/kg.

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

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

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

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

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

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

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 ^{13}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.

MUTAGENICITY

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.

REPRODUCTION AND TERATOLOGY

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

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PART III: CONSUMER INFORMATION

[Pr]VAN-Pantoprazole
pantoprazole sodium

This leaflet is part III of a three-part "Product Monograph" published when VAN-Pantoprazole was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VAN-Pantoprazole. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
VAN-Pantoprazole is used to treat acid-related stomach problems such as stomach ulcers (also known as gastric ulcers), duodenal ulcers (including ulcers that are associated with a bacterium called *Helicobacter pylori)*, reflux esophagitis (a severe form of heartburn), symptoms of gastro-esophageal reflux disease (heartburn and acid regurgitation), and the prevention of gastrointestinal damage (such as erosions and/or ulcers in the stomach /duodenum) and symptoms caused by non-steroidal anti-inflammatory drugs [(NSAIDs) medicines commonly used to treat arthritis and certain muscle conditions] when individuals must continue to take NSAIDs and where these individuals are considered to have an increased risk of developing gastrointestinal damage.

What it does:
VAN-Pantoprazole works by reducing the amount of acid made in your stomach.

When it should not be used:
You should not take VAN-Pantoprazole if you think you might be allergic to any of the ingredients (see "**What the non-medicinal ingredients are"**).

What the medicinal ingredient is:
pantoprazole sodium

What the non-medicinal ingredients are:
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) and opadry yellow contains: lecithin (soy), titanium dioxide, yellow iron oxide, polyvinyl alcohol, talc and xanthan gum).

What dosage forms it comes in:
- Delayed-Release Tablet, 40 mg pantoprazole

BEFORE you use VAN-Pantoprazole talk to your doctor or pharmacist:
- about all health problems you have now or have had in the past, including liver problems;
- about all other medicines you take, including ones you can get without a prescription
- if you are taking atazanavir sulphate (Reyataz) advise your doctor as this may interact with VAN-Pantoprazole.
- if you are allergic to pantoprazole or to the non-medicinal ingredients which are present in VAN-Pantoprazole
- if you are pregnant, plan to become pregnant or are breastfeeding. Excretion into human milk has been reported, discuss this with your doctor.
- if you suffer unexplained weight loss, recurrent vomiting or vomiting blood, dark stools, fatigue (anemia) or difficulty in swallowing
- If you have severe and/or persistent diarrhea, because products which reduce stomach acid have been associated with a small increase in infectious diarrhea
- if you experience any cardiovascular (e.g. heart) or neurological (e.g. brain) symptoms including palpitations (rapid heartbeat), dizziness, seizures, and tetany (muscle condition with symptoms such as twitching, spasms, cramps and convulsions) as these may be signs of hypomagnesaemia (low magnesium levels in the body)

People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist or spine. You should take VAN-Pantoprazole exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take VAN-Pantoprazole.

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor or pharmacist if you are taking warfarin. Warfarin may interact with VAN-Pantoprazole.

VAN-Pantoprazole may interact with atazanavir sulphate (Reyataz).

PROPER USE OF THIS MEDICATION

Usual adult dose:
Your doctor will have explained why you need to be treated with VAN-Pantoprazole and will have told you what dose to take. Follow your doctor's directions carefully as they may be different from the information provided in this leaflet.

IMPORTANT: PLEASE READ

WARNINGS AND PRECAUTIONS

VAN-Pantoprazole should be taken in the morning, with or without food. Swallow the tablet(s) whole, with water. Do not crush or chew the tablet(s).

VAN-Pantoprazole may be used in combination with two antibiotics to treat ulcers associated with *Helicobacter pylori*. Doses of VAN-Pantoprazole and each of the antibiotics should be taken twice a day, or as prescribed by your doctor.

Overdose:

In case of drug overdose, contact a healthcare professional (e.g. doctor), hospital emergency department or regional Poision Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take one dose of VAN-Pantoprazole, take a tablet as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never double-up on a dose to make up for the one you have missed, just go back to your regular schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT

Like any medication, VAN-Pantoprazole may cause side effects in some people. When side effects have been reported, they have been generally mild and did not last a long time. Headache, diarrhea and nausea are the most common side effects; less often rash, itchiness and dizziness can occur. If any of these become troublesome, consult your doctor. If you experience any unusual or unexpected symptoms while using VAN-Pantoprazole, consult your doctor.

After stopping your medication, your symptoms may get worse and your stomach may increase the acid production.

Treatment in combination with antibiotics:

If you experience symptoms such as severe (watery or bloody) diarrhea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this happens, stop taking these drugs and call your healthcare professional immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Stop taking drug and call your doctor or pharmacist
Rare	Disturbances in vision*	√
Isolated cases	Liver damage (symptoms include yellowing of the skin and eyes)	√
Isolated Cases	Severe skin reactions such as, Stevens-Johnson-Syndrome, Erythema multiforme, Exfoliative dermatitis, Toxic epidermal necrolysis, Photosensitivity	√
Isolated Cases	Muscle wasting	√

This is not a complete list of side effects. For any unexpected effects while taking VAN-Pantoprazole, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your tablets at room temperature (15°C to 30°C) in the recommended packaging and in a safe place, where children cannot reach them.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals. This leaflet was prepared by

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