PRODUCT MONOGRAPH

Pr TECTA®

pantoprazole enteric-coated tablets, 40 mg

(as pantoprazole magnesium)

H+, K+-ATPase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	Enteric-Coated Tablet 40 mg pantoprazole (as pantoprazole magnesium)	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

Note: As with all proton pump inhibitors, when TECTA® (pantoprazole magnesium) 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

TECTA® (pantoprazole magnesium) 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).
- *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*

Pediatrics:

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

Geriatrics (> 65years of age):

No dosage 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.

CONTRAINDICATIONS

Patients who are hypersensitive to pantoprazole, substituted benzimidazoles, 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.

Co-administration with rilpivirine is contraindicated.

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 TECTA® (pantoprazole magnesium) is instituted since treatment with pantoprazole magnesium 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.

Bone Fracture

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

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.

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 2Cl9.

Rilpivirine
Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir and Nelfinavir
Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ® and VIRACEPT® Product Monographs).

If the combination of TECTA® 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 TECTA® should not exceed an equivalent dose of omeprazole of 20 mg daily (see REYATAZ® Product Monograph).

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

Hepatic/Biliary/Pancreatic & Renal

Pantoprazole 40 mg daily is not recommended in patients with severe liver disease. For more details please 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.

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 TECTA®. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

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. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

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

The chronic use of PPIs may lead to hypomagnesemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

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.

Interference with 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, TECTA® treatment should be stopped 14 days before CgA measurements (see DRUG INTERACTIONS).

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. TECTA® (pantoprazole magnesium) should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus. See also REPRODUCTION AND TERATOLOGY.

Nursing Women:

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

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

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

No differences in adverse reactions are expected between pantoprazole magnesium and pantoprazole sodium.

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.

In a short term study (40 mg pantoprazole magnesium tablet, once daily for 7 days) in patients with GERD, and in a 4 to 8-week clinical trial in 636 GERD patients, the adverse event profile seen with TECTA® (pantoprazole magnesium) 40 mg tablet was similar to that seen with the pantoprazole sodium 40 mg tablet.

No differences in adverse reactions are expected between pantoprazole magnesium and pantoprazole sodium.

Adverse events have been recorded during controlled clinical investigations in 13000 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 sodium 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.

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

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

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

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

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 (20 mg or 40mg pantoprazole sodium once daily) in short-term clinical trials (duration of up to 3 months).

Adverse Events with a frequency of 0.1 to 1% related to pantoprazole sodium 20mg or 40mg

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 sodium therapy (20 mg or 40 mg once daily) in short-term and long-term clinical trials.

Adverse Events with a frequency of >1%, 20 or 40 mg pantoprazole sodium

Influenza like illness, Headache, Diarrhea

Adverse Events with a frequency of 0.1 to 1%, 20 or 40 mg pantoprazole sodium

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, Hemmorrhoids, Pain, Flatulence, Viral infection, Hypertriglyceridemia, Toothache, Hypersensitivity, Rash, Abdominal pain lower, Pneumonia, Abdominal distension, Dyspnoea, Muscle cramp, Rhinitis, Peripheral Edema, Tonsilitis, Angina Pectoris, Cholelithiasis, Sinus congestion, Influenza, Vertigo, Insomnia, Infection, Osteoarthritis, Hypercholesterolemia, Pruritus, Eczema, Sleep Disorder, Migraine, Aspartate aminotransferase increased, Hyperglycemia, Musculoskeletal discomfort, Blood triglycerides Increased, Myocardial infarction, Tendonitis, Weight increased, Rectal hemmorrhage, Cystitis, Nasal congestion, Arthritis, Contusion, Abdominal discomfort, Enteritis

The following serious adverse events regardless of causality were reported with a frequency of <0.1% in either 20 mg or 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%)

Liver/Biliary: 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 Laboratory Parameters portions of the ADVERSE REACTION section, the ACTION & CLINICAL PHARMACOLOGY Special Populations & Conditions sections, 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; Hyponatremia; Hypomagnesemia; 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; Hyperlipidemias and lipid increases (triglycerides, cholesterol); Weight changes; Body temperature increased; Edema peripheral; Gynecomastia; 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.

There have been post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (See **WARNINGS AND PRECAUTIONS, Immune**).

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).

Drug-Drug Interactions

The magnesium content of a 40 mg tablet is negligibly low and thus far below the amount of magnesium taken with food or dietary supplements. No differences in drug-drug interactions are expected between pantoprazole magnesium and pantoprazole sodium.

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 sodium 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.

Rilpivirine
Co-administration is contraindicated due to significant decreases in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir
Co-administration of TECTA® with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma Cmax and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir. (see REYATAZ® Product Monograph).

Nelfinavir
Co-administration of TECTA® with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and Cmax for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively) (see VIRACEPT® Product Monograph).

Saquinavir
Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities (see the INVIRASE® Product Monograph).

Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and Cmax by 75%.

Drug-Food Interactions

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

Drug-Laboratory Interactions

There have been reports of false-positive results in urine screening tests for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. To some extent, a cross-reactivity of proton pump inhibitors to the THC assay in the OnTrak TesTcard™ 9 has been seen, though this may not be limited to this screening

test. In order to verify positive urine screening results, a confirmatory method should be considered.

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, TECTA® treatment should be stopped 14 days before CgA measurements (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Pharmacodynamic Properties).

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 TECTA® (pantoprazole magnesium) for the oral treatment of duodenal ulcer is 40 mg 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 TECTA® (pantoprazole magnesium) 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 TECTA® (pantoprazole magnesium) 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 TECTA® (pantoprazole magnesium) 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 TECTA® (pantoprazole magnesium) 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 TECTA® (pantoprazole magnesium) 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.
Patients with healed gastroesophageal reflux disease, who require greater than usual maintenance doses of PPIs to avoid recurrence of reflux esophagitis, may consider 40 mg TECTA® 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

TECTA® (pantoprazole magnesium) 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, consult your regional Poison Control Centre.

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 sodium 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

TECTA® (pantoprazole magnesium) 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).

Fasting gastrin values increased during pantoprazole sodium treatment, but in most cases the increase was only moderate. An extensive evaluation of clinical laboratory results has not revealed any clinically important changes during pantoprazole sodium treatment (except for gastrin which increased to 1.5-fold after 4 to 8 weeks).

Treatment with pantoprazole sodium 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 sodium was administered concomitantly with combinations of amoxicillin, clarithromycin, and/or metronidazole. When a single dose of pantoprazole sodium 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

Daily oral doses of pantoprazole magnesium 40 mg tablet showed a consistent and effective acid control. Information from a pharmacodynamic trial in patients with GERD indicates that TECTA® (pantoprazole magnesium) 40 mg tablets demonstrate similar 24-hour inhibition of acid secretion, and effect on intragastric pH, as pantoprazole sodium 40 mg tablets (See HUMAN PHARMACOLOGY).

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 WARNINGS AND PRECAUTIONS, Interference with Laboratory Tests).

Pharmacokinetics

Pantoprazole magnesium and pantoprazole sodium are not bioequivalent in terms of plasma AUC and C_{max}. In healthy, adult male volunteers, kinetic studies comparing the two salts show that the AUC of pantoprazole magnesium is almost 100% relative to that of pantoprazole sodium, under both fed and fasted conditions. C_{max} is lower for pantoprazole magnesium (approximately 65 – 73% of pantoprazole sodium values).

Absorption: Pantoprazole magnesium is absorbed rapidly following administration of a 40 mg enteric-coated tablet. Following an oral dose of 40 mg, mean maximum serum concentrations of approximately 1.3 μg/mL and 1.4μg/mL are reached after about 2.5 and 6 hours under fasting and fed conditions respectively. The AUC is approximately 4 μg.h/mL.

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 sodium 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, 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 sodium 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 sodium 40 mg. After a single oral dose of pantoprazole sodium 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 sodium. 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 sodium, 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.

Renal Insufficiency:

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole sodium 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 15ºC to 30ºC in the recommended packaging.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

TECTA® (pantoprazole magnesium) is available as enteric-coated tablets for oral administration. The tablets are yellow, round, biconvex tablets marked 40 on one side and contain 40 mg pantoprazole. Tablets are available in bottles of 100 or 7 tablets, and in blisters of 7 and 30 tablets.

Not all pack sizes may be marketed.

Non-medicinal Ingredients: Anhydrous Sodium Carbonate, Mannitol, Crospovidone, Povidone, Calcium Stearate, Hypromellose, Titanium Dioxide, Ferric Oxide, Propylene Glycol, Poly (ethylacrylate, methacrylic acid), Triethyl Citrate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

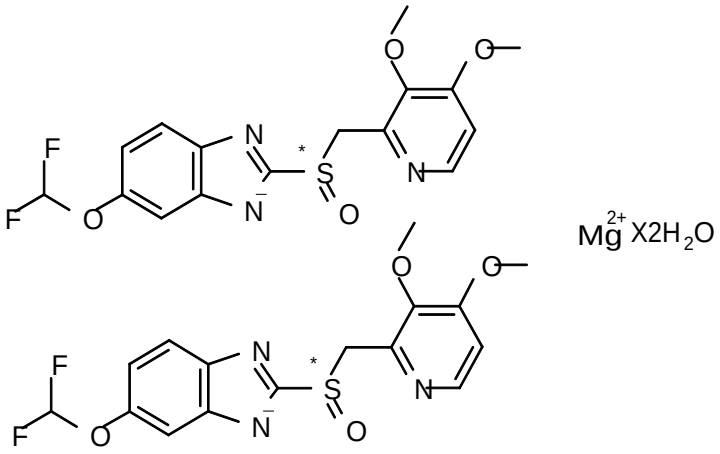
Drug Substance

Proper name: Pantoprazole magnesium

Chemical name: magnesium bis [5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl) - methyl]-sulfiny1]-1-H-benzimidazolide] dihydrate

Molecular formula and molecular mass: $C_{32}H_{28}F_4MgN_6O_8S_2 \times 2H_2O$ Mr: 825.08

Structural formula:



Physicochemical properties:

Physical description: White to beige powder

Solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, dilute acids, etc.):

Solvent	**Concentration**
Water (pH 8.24 - 8.74) (37 ºC)	C_s=(3.39±0.50) x 10-4 Mol/l
Buffer (pH 6.83-6.92) (37 ºC)	C_s =(5.99±0.18) x 10-4 Mol/l
Buffer pH 7.4 (37 ºC)	C_s =(6.70±0.44) x 10-4 Mol/l
Buffer pH 11 (37 ºC)	C_s =(9.98±0.46) x 10-4 Mol/l
Methanol (22-24 ºC)	C_s =(3.58±0.04) x 10-2 Mol/l
Ethanol (22-24 ºC)	C_s =(3.63±0.14) x 10-3 Mol/l
Acetone (22-24 ºC)	C_s =(7.79±0.21) x 10-5 Mol/l
Acetonitrile (22-24 ºC)	C_s =(3.46±0.27) x 10-5 Mol/l
N-hexane (22-24 ºC)	C_s <1.54x10-7 Mol/l

pH and pKa values: The following pKa-values have been determined at 25°C, as follows:

Pka1 = 8.11 ± 0.02 (n = 7)

Pka2 = 3.77 ± 0.02 (n = 7)

Other: Partition coefficient in octanol / water :

LogD 7.4 = log [c(octanol) / c (H_2O)] = 2.02 ± 0.01 (n=3)

CLINICAL TRIALS

A double-blind, randomized, parallel group clinical study comparing 40 mg pantoprazole magnesium to 40 mg pantoprazole sodium was performed in 636 patients with GERD grades 1 – 3 (Savary-Miller classification, modified by Siewert). The primary variable was endoscopically confirmed healing of reflux esophagitis after 8 weeks of treatment with either pantoprazole magnesium or pantoprazole sodium. Pantoprazole magnesium 40 mg o.d. was proven to be comparable to pantoprazole sodium 40 mg o.d. with respect to endoscopic healing after 8 weeks of treatment (with healing rates for the ITT population of 87.3% and 85.0% respectively). After 4 weeks of treatment, the healing rates for pantoprazole magnesium and pantoprazole sodium in the ITT population were 72.7% and 66.2% respectively. This represents a statistically significant difference.

Table 1: Healing rates (%) after 4 weeks

Population	Pantoprazole-Mg	Pantoprazole-Na	Difference	95% CI of difference
ITT[1]-population (N) Healing rate (%) (95% confidence interval)	N=322 patients 72.7 (67.5; 77.5)	N=314 patients 66.2 (60.7; 71.5)	6.4	(0.43; 12.43)
PP[2]-population (N) Healing rate (%) (95% confidence interval)	N=271 patients 77.9 (72.4; 82.7)	N=261 patients 71.6 (65.8; 77.0)	6.2	(0.03; 12.40)

[1]ITT=Intention to Treat
[2]PP=Per Protocol
Non-inferiority determined when the confidence interval for the difference between the two healing rates is completely above the non-inferiority margin of -10%.

Table 2: Healing rates (%) after 8 weeks

Population	**Pantoprazole-Mg**	**Pantoprazole-Na**	**Difference**	**95% CI of difference**
ITT[1]-population (N) **Healing rate (%)** (95% confidence interval)	N=322 patients **87.3** (83.1; 90.7)	N=314 patients **85.0** (80.6; 88.8)	**2.2**	**(-2.3; 6.7)**
PP[2]-population (N) **Healing rate (%)** (95% confidence interval)	N=271 patients **91.9** (88.0; 94.8)	N=261 patients **91.2** (87.1, 94.3)	**0.7**	**(-3.3; 4.7)**

[1]ITT=Intention to Treat
[2]PP=Per Protocol
Non-inferiority determined when the confidence interval for the difference between the two healing rates is completely above the non-inferiority margin of -10%.

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.

Based upon the similar inhibition of acid secretion and effect on intragastric pH as pantoprazole sodium, TECTA® (pantoprazole magnesium) is expected to have similar daytime and night-time relief of symptoms.

***Helicobacter pylori* associated duodenal ulcer**

Table 3: 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 sodium 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 sodium 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%

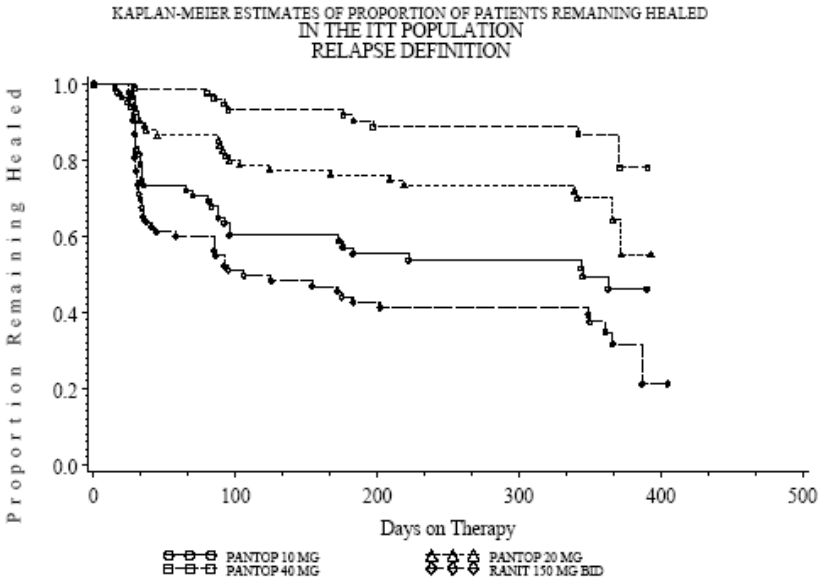
ITT + kpa: Patients who were *H. pylori* positive at the initial examination and had complete and valid results for the requisite (based on the study) number of tests at the appropriate follow-up visit. In study 1, 3 of 4 *H. pylori* tests must be complete and valid.
Study 1: Patients with active duodenal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

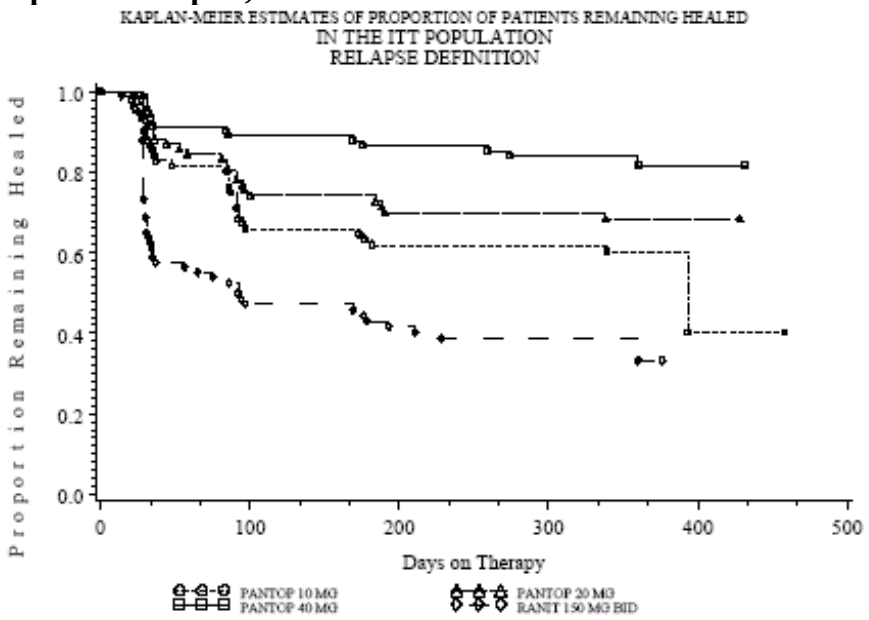
The long-term maintenance of healing of erosive esophagitis was assessed in two U.S. randomised, double-blind, parallel-group, active controlled studies. Eligible patients in both studies had a recent history of grade II or III (Hetzel-Dent) erosive esophagitis, and endoscopically demonstrated healing.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

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 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.

DETAILED PHARMACOLOGY
ANIMAL PHARMACOLOGY

Pharmacodynamics:

In vivo, pantoprazole sodium produced marked and long-lasting inhibition of basal and stimulated gastric acid secretion with median effective dose (ED50) values ranging from 0.2 - 2.4 mg/kg in rats and dogs. In addition to the administration of single doses, pantoprazole sodium 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 sodium showed antiulcer activity.

In parallel to the profound inhibition of gastric acid secretion, pantoprazole sodium 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 sodium, 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 sodium 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 sodium, 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 sodium 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 sodium; only doses over 300 mg/kg prolonged the effects of diazepam.

Pharmacokinetics:

The pharmacokinetic characteristics of pantoprazole sodium (40 mg) and pantoprazole magnesium (40 mg) tablets were compared in a study in dogs. Male beagle dogs received a single oral dose in the form of uncoated tablets of either drug and blood samples were taken before and after administration. A sodium bicarbonate solution was administered together with the tablets to prevent degradation of pantoprazole in the stomach.

The ratio of the AUCs of the 40 mg pantoprazole magnesium tablet to the 40 mg pantoprazole sodium tablet was 86% and the corresponding value for C_{max} was 62%. Thus, when equal doses were administered, the systemic exposure to pantoprazole was lower after administration of the magnesium than after the sodium salt. The terminal half-life ($t_{1/2}$) of pantoprazole magnesium 40 mg was longer by approximately 23% compared to that of pantoprazole sodium. No difference in t_{max} between the two forms of pantoprazole was apparent.

Absorption and Distribution

Pantoprazole sodium 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 sodium, 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 sodium 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 sodium. 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:

A pharmacodynamic trial in patients with GERD (n=79) was performed to study the effect of pantoprazole magnesium and pantoprazole sodium on 24-hour intragastric pH. The primary objective of this study was to compare the 24-hour intragastric pH profile under steady-state conditions following administration of pantoprazole magnesium versus pantoprazole sodium administered as a 1 x 40 mg enteric-coated tablet once daily for 7 consecutive days each in adult symptomatic GERD patients (Savary-Miller stage I-III). The primary criterion for efficacy was the percentage of time with intragastric pH>4.

Results from this trial indicate that TECTA® (pantoprazole magnesium) 40 mg tablets demonstrate similar inhibition of acid secretion (day and night), and effect on intragastric pH, as pantoprazole sodium 40 mg tablets.

Table 4: Equivalence Analysis Pantoprazole Mg vs. Pantoprazole Na

	Difference[1]	95% C.I.[2]	Acceptance Region[3]	Intra-Subject CV (%)	Inter- Subject CV (%)
H. Pylori negative subjects	-2.40	-4.99 to 0.18	(-5.12, 5.12)	18.15 %	29.74 %
H. Pylori positive subjects	-0.60	-7.20 to 6.01	(-10.69, 10.69)	12.29 %	19.16 %

CV – co-efficient of variation
[1] Calculated using least-squares means (untransformed data)
[2] 95% Classic confidence interval for difference (untransformed data)
[3] Acceptance region defined as +/- 15% of the Reference least-squares mean

Pantoprazole is a potent inhibitor of gastric acid secretion. This was demonstrated with pantoprazole sodium 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 sodium 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 sodium 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 sodium 40 mg was significantly superior to standard H2-blocker therapy (300 mg ranitidine at night) with regard to median 24-hour and daytime pH; however, not for nighttime measurements.

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

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

* $p<0.05$ vs ranitidine

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

Table 7: Effect of oral pantoprazole sodium 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:

Maximum serum concentrations of pantoprazole magnesium are reached within approximately 2.5 hours after oral intake. Following a dose of 40 mg, mean maximum serum concentrations of approximately 1.3 µg/mL and 1.4µg/mL are reached after about 2.5 and 6 hours under fasting and fed conditions respectively. 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 sodium 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. The absolute bioavailability of the pantoprazole sodium tablet is 77%.

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 sodium 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 sodium 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 8 below).

Table 8: 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 sodium 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 9 below).

Table 9: 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 108 - 109 bacteria per animal. Starting on Day 8, the mice were treated three times daily with placebo or active drug (pantoprazole sodium 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 10: 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 sodium 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 sodium 100 mg/kg tid + amoxicillin 0.5 mg/kg tid (n=10)	100%
Pantoprazole sodium 100 mg/kg tid + clarithromycin 0.5 mg/kg tid (n=10)	90%
Pantoprazole sodium 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 sodium alone was without effect on Helicobacter felis infection, while in combination therapy with the antibiotics, pantoprazole sodium had a potentiating effect on the elimination rate of Helicobacter felis infection. The results show a potentiation by a factor of about six, i.e., pantoprazole sodium 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 single dose rodent (rat and mice) studies with pantoprazole magnesium, no toxic effects were noted under any of the doses administered (100, 300, 1000 mg/kg).

In acute toxicity studies in mice the mean lethal dose (LD50) values for pantoprazole sodium were found to be greater than 370mg/kg bodyweight for i.v. administration and over 700 mg/kg bodyweight for oral administration.

In the rat the corresponding values were greater than 240mg/kg for i.v. administration and greater than 900mg/kg for oral administration.

In general, therefore, higher doses of pantoprazole magnesium than of the sodium salt were tolerated by both rats and mice in single dose studies.

Table 11: Acute toxicity studies with pantoprazole sodium

Species	Route	Sex	Lethal dose mg/kg
Mouse	p.o.	M	>945
		F	707
	i.v.	M	377
		F	374
Rat	p.o.	M	1191
		F	919
	i.v.	M	293
		F	242
Dog	p.o.	M/F	266-887
	i.v.	F/F	133-266

Doses in terms of the free compound

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

Pantoprazole magnesium was administered orally once daily to groups of 10 male/10 female rats at doses of 0, 50 and 200 mg/kg/day for 4 weeks. As a comparison, pantoprazole sodium was administered once daily to groups of 10 male/10 female rats at the same doses (50 and 200 mg/kg/day). For toxicokinetic analysis, further groups of 2 males/2 females or 6 males/6 females were treated with pantoprazole magnesium at 0, 50 or 200 mg/kg/day or with pantoprazole sodium at 50 or 200 mg/kg/day, with blood samples taken on Day 1, 7 and in the 4th test week.

No qualitative or quantitative differences in the pattern of toxic effects were observed in rats after repeated administration of equal doses of pantoprazole as a magnesium or sodium salt. No remarkable differences in the toxicokinetic characteristics between the two salt forms were detected in rats.

Daily oral doses of pantoprazole sodium 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 of pantoprazole sodium 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 sodium 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 sodium, 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 sodium 16 mg/kg
Group 2 - clarithromycin 75 mg/kg + metronidazole 50 mg/kg
Group 3 - pantoprazole sodium 16 mg/kg + amoxicillin 120 mg/kg + metronidazole 50 m/kg
Group 4 - pantoprazole sodium 16 mg/kg + amoxicillin 120 mg/kg + clarithromycin 50 mg/kg
Group 5 - pantoprazole sodium 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 13C-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 sodium.

Carcinogenicity

Three carcinogenicity studies had been conducted with pantoprazole sodium:

- 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 sodium, 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 sodium 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 sodium 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, with treatment of 40 - 80 mg of pantoprazole sodium for 1 year, 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 sodium 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 sodium 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 human dose (i.e., 40 mg dose). The effect of pantoprazole sodium 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 sodium.

Tumors induced in rats and mice by pantoprazole sodium 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 sodium 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 sodium was 2.5 times higher than that in humans.

Mutagenicity

Pantoprazole sodium was studied in several mutagenicity studies: Pantoprazole sodium was found negative in the Ames test, 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. In addition, the potential of pantoprazole sodium 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 sodium 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 sodium 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 sodium 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 is no experience with the use of pantoprazole during pregnancy.

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PART III: PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTECTA®
pantoprazole enteric-coated tablets (as pantoprazole magnesium)

Read this carefully before you start taking TECTA® 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 TECTA®.

What is TECTA® used for?
TECTA® is used to treat acid-related stomach 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*).**
  TECTA® is used in combination with two antibiotics.
- **Reflux esophagitis.**
  This is a severe form of heartburn.
- **Symptoms of gastro-esophageal reflux disease.**
  The symptoms include heartburn and acid regurgitation. GERD is a condition in which stomach acid backs up into your esophagus.

How does TECTA® work?
TECTA® is a proton pump inhibitor. It reduces the amount of acid your stomach makes.

What are the ingredients in TECTA®?
Medicinal ingredients: pantoprazole magnesium.
Non-medicinal ingredients: Anhydrous Sodium Carbonate, Calcium Stearate, Crospovidone, Ferric Oxide, Hypromellose, Mannitol, Povidone, Propylene Glycol, Poly (ethylacrylate, methacrylic acid), Titanium Dioxide, Triethyl Citrate.

TECTA® comes in the following dosage forms:
- Tablet, 40 mg.

Do not use TECTA® if:
- You are allergic to TECTA® or any of its ingredients. (See **What are the ingredients in TECTA®?**).
- You are taking rilpivirine.

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

- are taking other medications (see **The following may interact with TECTA®)**.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breast feed. Pantoprazole has been found in human breast milk. Talk with your doctor.
- 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 TECTA® exactly as prescribed. You will use the lowest dose and shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

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

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

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

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 TECTA®:
Warfarin, atazanavir, nelfinavir, saquinavir/ritonavir, methotrexate.

How to take TECTA®:

- Take TECTA® in the morning.
    - with or without food.
    - before breakfast, is recommended.
- Swallow the tablet(s) whole with water.
- Do not crush or chew the tablet(s).

Usual adult dose:

Your doctor will have told you what dose to take for your condition. Follow your doctor's

directions carefully as they may be different from the information provided in this leaflet.

Keep taking TECTA® until you have finished all your tablets. Do not stop even when you start to feel better. If you stop taking TECTA® too soon, your symptoms may return.

TECTA® may be used in combination with two antibiotics to treat ulcers caused by *H. pylori*. TECTA® and both antibiotics are to be taken twice a day, or as prescribed by your doctor.

Overdose:

If you think you have taken too much TECTA®, contact your 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 TECTA®?

Like all medication, TECTA® 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 feel when taking TECTA®.

The most common side effects are:

- headache
- diarrhea
- nausea

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

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

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
RARE. Disturbances in vision. Most cases reported are not serious.			✓
ISOLATED CASES. 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.			✓
Clostridium difficile colitis (bowel inflammation). Symptoms include severe			✓

(watery or bloody) diarrhea, fever, and abdominal pain or tenderness.			

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).
- By calling 1-866-234-2345 (toll-free).
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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 TECTA® at room temperature, 15°- 30°C.
Keep out of reach and sight of children.

If you want more information about TECTA®:

- 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(http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.takedacanada.com, or by calling 1-866-295-4636.

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