SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
INN Name: Pantoprazole Sodium Delayed Release Tablets USP 20 mg
Trade Name: PANTIN 20
Strength: 20 mg
Pharmaceutical form: Tablet

2. Qualitative and quantitative composition
Each Delayed Release tablet contains Pantoprazole Sodium Sesquihydrate USP equivalent to Pantoprazole 20 mg
Excipients: Each 20 mg tablet contains 51.02 mg of Lactose monohydrate.

3. Pharmaceutical form
Dosage form: Delayed-Release tablet
Description: Yellow to pale yellow, oval, biconvex, delayed-release tablets imprinted "H125" on one side with black ink and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Pantoprazole Sodium Delayed-Release Tablets indicated for:
Short-term treatment of erosive esophagitis associated with gas Troesophageal Reflux Disease (GERD)
Pantoprazole Sodium Delayed-Release Tablets is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE). For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of Pantoprazole Sodium Delayed-Release Tablets 40mg may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.
Maintenance of Healing of Erosive Esophagitis
Pantoprazole Sodium Delayed-Release Tablets 40 mg is indicated for maintenance of healing of EE and reduction in relapse rates of daytime and Night time heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

Pathological Hypers ecretory Conditions Including Zollinger-Ellis on Syndrome
Pantoprazole Sodium Delayed-Release Tablets is indicated for the long-term treatment of pathological hypersecretory conditions,including Zollinger-Ellison (ZE) Syndrome.

4.2 Posology and method of administration

Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.
Recommended dose

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

* For adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of Pantoprazole Sodium Delayed-Release Tablets may be considered.

† Controlled studies did not extend beyond 12 months

‡ Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.

4.3 Contraindications

Pantoprazole Sodium Delayed-Release Tablets is contraindicated in patients with known hypersensitivity to any component of the formulation or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

Proton pump inhibitors (PPIs), including Pantoprazole Sodium Delayed-Release Tablets are contraindicated with rilpivirine-containing products

4.4 Special warnings and precautions for use

Presence of Gastric Malignancy

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

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including Pantoprazole Sodium Delayed-Release Tablets. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Pantoprazole Sodium Delayed-Release Tablets if acute interstitial nephritis develops.

Clostridium difficile-Associated Diarrhoea

Published observational studies suggest that PPI therapy like Pantoprazole Sodium Delayed-Release Tablets may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve

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

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

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematous cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Pantoprazole Sodium Delayed-Release Tablets, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Cyanocobalamin (Vitamin B-12) Deficiency

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

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

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

Tumorigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of Pantoprazole Sodium Delayed-Release Tablets. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown [see 4.1]

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Interference with Investigations for Neuroendocrine Tumours

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop Pantoprazole Sodium Delayed-Release Tablets treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Interference with Urine Screen for THC

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including Pantoprazole Sodium Delayed-Release Tablets.

Concomitant Use of Pantoprazole Sodium Delayed-Release Tablets with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients

Excipients:

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Table includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Pantoprazole Sodium Delayed-Release Tablets and instructions for preventing or managing them.

Antiretrovirals	
Clinical Impact	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. o Decreased exposure of some antiretroviral drugs (e.g., rilpivirine atazanavir, and nelfinavir) when used concomitantly with

	pantoprazole may reduce antiviral effect and promote the development of drug resistance. o Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity of the antiretroviral drugs. There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.
Intervention	Rilpivirine-containing products: Concomitant use with Pantoprazole Sodium Delayed-Release Tablets is contraindicated See prescribing information. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with Pantoprazole Sodium Delayed-Release Tablets See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
Methotrexate	
Clinical Impact:	Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted
Intervention	A temporary withdrawal of Pantoprazole Sodium Delayed-Release Tablets may be considered in some patients receiving high-dose methotrexate.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	

Clinical Impact:	Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving Pantoprazole Sodium Delayed-Release Tablets and MMF. Use Pantoprazole Sodium Delayed-Release Tablets with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors
Intervention:	Temporarily stop Pantoprazole Sodium Delayed-Release Tablets treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs
Intervention:	An alternative confirmatory method should be considered to verify positive results.
Clopidogrel	
Clinical Impact:	Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition
Intervention:	No dose adjustment of clopidogrel is necessary when administered with an approved dose of Pantoprazole Sodium Delayed-Release Tablets.

4.6 Pregnancy and lactation

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats at oral pantoprazole doses up to 450 mg/kg/day (about 88 times the recommended human dose based on body surface area) and in rabbits at oral doses up to 40 mg/kg/day (about 16 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals. The studies have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in humans at a dose of 40 mg). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in humans receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses.

There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of fetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose of pantoprazole sodium. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole sodium in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Paediatric Use

The safety and effectiveness of Pantoprazole Sodium Delayed-Release Tablets for short-term treatment (up to eight weeks) of EE associated with GERD have been established in paediatric patients 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, Pantoprazole Sodium Delayed-Release Tablets is indicated for the short-

term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of Pantoprazole Sodium Delayed-Release Tablets for paediatric uses other than EE have not been established.

1 year through 16 years of age

Use of Pantoprazole Sodium Delayed-Release Tablets in paediatric patients 1 year through 16 years of age for short-term treatment (up to eight weeks) of EE associated with GERD is supported by: a) extrapolation of results from adequate and well-controlled studies that supported the approval of Pantoprazole Sodium Delayed-Release Tablets for treatment of EE associated with GERD in adults, and b) safety, effectiveness, and pharmacokinetic studies performed in paediatric patients [see Clinical Studies (14.1), Clinical Pharmacology (12.3)].

Safety of Pantoprazole Sodium Delayed-Release Tablets in the treatment of EE associated with GERD in paediatric patients 1 through 16 years of age was evaluated in three multicentre, randomized, double-blind, parallel-treatment studies, involving 249 paediatric patients, including 8 with EE (4 patients ages 1 year to 5 years and 4 patients 5 years to 11 years). The children ages 1 year to 5 years with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥2) were treated once daily for 8 weeks with one of two dose levels of Pantoprazole Sodium Delayed-Release Tablets (approximating 0.6 mg/kg or 1.2 mg/kg). All 4 of these patients with EE were healed (Hetzel-Dent score of 0 or 1) at 8 weeks. Because EE is uncommon in the paediatric population, predominantly paediatric patients with endoscopically-proven or symptomatic GERD were also included in these studies. Patients were treated with a range of doses of Pantoprazole Sodium Delayed-Release Tablets once daily for 8 weeks. For safety findings see Adverse Reactions. Because these paediatric trials had no placebo, active comparator, or evidence of a dose response, the trials were inconclusive regarding the clinical benefit of Pantoprazole Sodium Delayed-Release Tablets for symptomatic GERD in the paediatric population. The effectiveness of Pantoprazole Sodium Delayed-Release Tablets for treating symptomatic GERD in paediatric patients has not been established.

Although the data from the clinical trials support use of Pantoprazole Sodium Delayed-Release Tablets for the short-term treatment of EE associated with GERD in paediatric patients 1 year through 5 years, there is no commercially available dosage formulation appropriate for patients less than 5 years of age

In a population pharmacokinetic analysis, clearance values in the children 1 to 5 years old with endoscopically proven GERD had a median value of 2.4 L/h. Following a 1.2 mg/kg equivalent dose (15 mg for ≤12.5 kg and 20 mg for >12.5 to <25 kg), the plasma concentrations of pantoprazole were highly variable and the median time to peak plasma concentration was 3 to 6 hours. The estimated AUC for patients 1 to 5 years old was 37% higher than for adults receiving a single 40 mg tablet, with a geometric mean AUC value of 6.8 μg·hr/mL.

Neonates to less than one year of age

Pantoprazole Sodium Delayed-Release Tablets was not found to be effective in a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 129 paediatric patients 1 through 11 months of age. Patients were enrolled if they had symptomatic GERD based on medical history and had not responded to non-pharmacologic interventions for GERD for two weeks. Patients received Pantoprazole Sodium Delayed-Release Tablets daily for four weeks in an open-label phase, then patients were randomized in equal proportion to receive Pantoprazole Sodium Delayed-Release Tablets treatment or placebo for the subsequent four weeks in a double-blind manner. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week treatment-withdrawal phase. There was no statistically significant difference between Pantoprazole Sodium Delayed-Release Tablets and placebo in the rate of discontinuation.

In this trial, the adverse reactions that were reported more commonly (difference of ≥4%) in the treated population compared to the placebo population were elevated CK, otitis media, rhinitis, and laryngitis.
In a population pharmacokinetic analysis, the systemic exposure was higher in patients less than 1 year of age with GERD compared to adults who received a single 40 mg dose (geometric mean AUC was 103% higher in preterm infants and neonates receiving single dose of 2.5 mg of Pantoprazole Sodium Delayed-Release Tablets and 23% higher in infants 1 through 11 months of age receiving a single dose of approximately 1.2 mg/kg). In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03 to 3.2 L/hr).

These doses resulted in pharmacodynamic effects on gastric but not esophageal pH. Following once daily dosing of 2.5 mg of Pantoprazole Sodium Delayed-Release Tablets in preterm infants and neonates, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 60% at baseline to 80% at steady-state). Following once daily dosing of approximately 1.2 mg/kg of Pantoprazole Sodium Delayed-Release Tablets in infants 1 through 11 months of age, there was an increase in the mean gastric pH (from 3.1 at baseline to 4.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 32% at baseline to 60% at steady-state). However, no significant changes were observed in mean intraesophageal pH or % time that esophageal pH was <4 in either age group.

Because Pantoprazole Sodium Delayed-Release Tablets was not shown to be effective in the randomized, placebo-controlled study in this age group, the use of Pantoprazole Sodium Delayed-Release Tablets for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

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

4.7 Effects on ability to drive and use machines
Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machines.

4.8 Undesirable Effects
The adverse reaction profiles for Pantoprazole Sodium Delayed-Release Tablets (pantoprazole sodium) For Delayed-Release Oral Suspension and Pantoprazole Sodium Delayed-Release Tablets (pantoprazole sodium) Delayed-Release Tablets are similar.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Adults

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral Pantoprazole Sodium Delayed-Release Tablets (20 mg or 40 mg), 299 patients on an H2-receptor antagonist, 46 patients on another PPI, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table.

	Pantoprazole Sodium Delayed-Release Tablets (n=1473) %	Comparators (n=345) %	Placebo (n=82) %
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7.0	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3.0	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for Pantoprazole Sodium Delayed-Release Tablets in clinical trials with a frequency of ≤2% are listed below by body system:
Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial edema
Gastrointestinal: constipation, dry mouth, hepatitis
Hematologic: leukopenia, thrombocytopenia
Metabolic/Nutritional: elevated CK (creatine kinase), generalized edema, elevated triglycerides, and liver enzymes elevated
Musculoskeletal: myalgia
Nervous: depression, vertigo
Skin and Appendages: urticaria, rash, pruritus
Special Senses: blurred vision
Pediatric Patients
Safety of Pantoprazole Sodium Delayed-Release Tablets in the treatment of EE associated with GERD was evaluated in pediatric patient's ages 1 year through 16 years in three clinical trials. Safety trials involved pediatric patients with EE; however, as EE is uncommon in the pediatric population, 249 pediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. All adult adverse reactions to Pantoprazole Sodium Delayed-Release Tablets are considered relevant to pediatric patients. In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions include: URI, headache, fever, diarrhea, and vomiting, rash, and abdominal pain.
For safety information in patients less than 1 year of age see Use in Specific Populations.
Additional adverse reactions that were reported for Pantoprazole Sodium Delayed-Release Tablets in pediatric patients in clinical trials with a frequency of ≤4% are listed below by body system:
Body as a Whole: allergic reaction, facial edema
Gastrointestinal: constipation, flatulence, nausea
Metabolic/Nutritional: elevated triglycerides, elevated liver enzymes, elevated CK (creatine kinase)
Musculoskeletal: arthralgia, myalgia
Nervous: dizziness, vertigo
Skin and Appendages: urticaria
The following adverse reactions seen in adults in clinical trials were not reported in pediatric patients in clinical trials, but are considered relevant to pediatric patients: photosensitivity reaction, dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leukopenia, and blurred vision.

Zollinger-Ellison (ZE) Syndrome

In clinical studies of ZE Syndrome, adverse reactions reported in 35 patients taking Pantoprazole Sodium Delayed-Release Tablets 80 mg/day to 240 mg/day for up to 2 years were similar to those reported in adult patients with GER

The following adverse reactions have been identified during postapproval use of Pantoprazole Sodium Delayed-Release Tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are listed below by body system:
Gastrointestinal Disorders: fundic gland polyps
General Disorders and Administration Conditions: asthenia, fatigue, malaise
Hematologic: pancytopenia, agranulocytosis
Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure
Immune System Disorders: anaphylaxis (including anaphylactic shock), systemic lupus erythematosus
Infections and Infestations: Clostridium difficile associated diarrhea
Investigations: weight changes
Metabolism and Nutritional Disorders: hyponatremia, hypomagnesemia
Musculoskeletal Disorders: rhabdomyolysis, bone fracture
Nervous: ageusia, dysgeusia
Psychiatric Disorders: hallucination, confusion, insomnia, somnolence
Renal and Urinary Disorders: interstitial nephritis
Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal), angioedema (Quincke's edema) and cutaneous lupus erythematosus

4.9 Overdose
Experience in patients taking very high doses of Pantoprazole Sodium Delayed-Release Tablets (greater than 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile Pantoprazole Sodium Delayed-Release Tablets
Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive. Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: proton pump inhibitors
ATC code: A02B C02
Mechanism of action
Pantoprazole is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

5.2 Pharmacokinetic properties Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets are prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (Cmax) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

In extensive metabolizers with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (Cmax) is 2.5 µg/mL; the time to reach the peak concentration (tmax) is 2.5 h, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 µg·h/mL (range 1.4 to 13.3 µg·h/mL). Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6–14.0 L/h, and its apparent volume of distribution is 11.0–23.6 L.

Absorption
After administration of a single or multiple oral 40 mg doses of Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and Cmax was 2.5 µg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.
Administration of Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets with food may delay its absorption up to 2 hours or longer; however, the Cmax and the extent of pantoprazole absorption (AUC) are not altered. Thus, Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets may be taken without regard to timing of meals.
Administration of pantoprazole granules, 40 mg, with a high-fat meal delayed median time to peak plasma concentration by 2 hours. With a concomitant high-fat meal, the Cmax and AUC of pantoprazole granules, 40 mg, sprinkled on applesauce decreased by 51% and 29%, respectively. Thus, Pantoprazole Sodium Delayed-Release Tablets For Delayed-Release Oral Suspension should be taken approximately 30 minutes before a meal.

Distribution
The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.
Metabolism
Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Excretion
After a single oral or intravenous dose of 14C-labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.
Specific Populations
Geriatric Patients

Only slight to moderate increases in the AUC (43%) and Cmax (26%) of pantoprazole were found in elderly subjects (64 to 76 years of age) after repeated oral administration, compared with younger subjects.

Pediatric Patients

The pharmacokinetics of pantoprazole were studied in children less than 16 years of age in four randomized, open-label clinical trials in pediatric patients with presumed/proven GERD. A pediatric granule formulation was studied in children through 5 years of age, and Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets were studied in children older than 5 years.

In a population PK analysis, total clearance increased with increasing bodyweight in a non-linear fashion. The total clearance also increased with increasing age only in children under 3 years of age

Neonate through 5 Years of Age

Children and Adolescents 6 through 16 Years of Age

The pharmacokinetics of Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets were evaluated in children ages 6 through 16 years with a clinical diagnosis of GERD. The PK parameters following a single oral dose of 20 mg or 40 mg of Pantoprazole Sodium Delayed-Release Tablets tablets in children ages 6 through 16 years were highly variable (%CV ranges 40 to 80%). The geometric mean AUC estimated from population PK analysis after a 40 mg PANTOPRAZOLE SODIUM DELAYED-RELEASE TABLETS tablet in pediatric patients was about 39% and 10% higher respectively in 6 to 11 and 12 to 16 year-old children, compared to that of adults

	6–11 years (n=12)	12–16 years (n=11)
Cmax (μg/mL)*	1.8	1.8
tmax (h)†	2.0	2.0
AUC (μg·h/mL)*	6.9	5.5
CL/F (L/h)†	6.6	6.8

* Geometric mean values

† Median values

Male and Female Patients

There is a modest increase in pantoprazole AUC and Cmax in women compared to men. However, weight-normalized clearance values are similar in women and men.

In pediatric patients ages 1 through 16 years there were no clinically relevant effects of gender on clearance of pantoprazole, as shown by population pharmacokinetic analysis.

Patients with Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.

Patients with Hepatic Impairment

In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7–9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.

Drug Interaction Studies

Effect of Other Drugs on Pantoprazole

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In in vivo drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and

phenytoin [also a CYP3A4 inducer] and clopidogrel), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates), and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered.

Effect of Pantoprazole on Other Drugs

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. In a crossover clinical study, 66 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. On Day 5, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (geometric mean ratio was 86%, with 90% CI of 79 to 93%) when pantoprazole was coadministered with clopidogrel as compared to clopidogrel administered alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 μM ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

Mycophenolate Mofetil (MMF)

Administration of pantoprazole 40 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of pantoprazole to 12 healthy subjects in a cross-over study resulted in a 57% reduction in the Cmax and 27% reduction in the AUC of MPA. Transplant patients receiving approximately 2000 mg per day of MMF (n=12) were compared to transplant patients receiving approximately the same dose of MMF and pantoprazole 40 mg per day (n=21). There was a 78% reduction in the Cmax and a 45% reduction in the AUC of MPA in patients receiving both pantoprazole and MMF

Other Drugs

In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of the following drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, diclofenac, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl estradiol]). In other in vivo studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once-daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Antacids

There was also no interaction with concomitantly administered antacids.

Pharmacodynamics

Pantoprazole Sodium Delayed-Release Tablets For Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD and a history of EE. In this multicenter, pharmacodynamic crossover study, a 40 mg oral dose of Pantoprazole Sodium Delayed-Release Tablets for Delayed-Release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20–80 mg) or a single dose of intravenous (20–120 mg) pantoprazole in healthy subjects. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies, pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was >3 and >4. Treatment with 40 mg of pantoprazole produced significantly greater increases in gastric pH than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown in Table.

	Median pH on day 7			
Time	Placebo	20mg	40 mg	80 mg
8 a.m. – 8 a.m. (24 hours)	1.3	2.9*	3.8*†	3.9*†
8 a.m. – 10 p.m. (Day time)	1.6	3.2*	4.4*†	4.8*†
10 p.m. – 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo

† Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of EE in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of Pantoprazole Sodium Delayed-Release Tablets for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with Pantoprazole Sodium Delayed-Release Tablets Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following short-term treatment with Pantoprazole Sodium Delayed-Release Tablets elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible

to the proliferative effects of elevated gastrin concentrations produced by PPIs. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 m
Endocrine Effects

In a clinical pharmacology study, Pantoprazole Sodium Delayed-Release Tablets given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.
In a 1-year study of GERD patients treated with Pantoprazole Sodium Delayed-Release Tablets or 20 mg, there were no changes from baseline in overall levels of T3, T4, and TSH. onth off-dose recovery
Pharmacogenomics
CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10 hours in adults, they still have minimal accumulation (23% or less) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.
Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

5.3 Preclinical safety data
Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. In the two-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the fore-stomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year studies, an increased number of liver tumours were observed in rats and in female mice, and was interpreted as being due to pantoprazole's high metabolic rate in the liver. A slight increase in neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected in animal reproduction studies, signs of slight feto toxicity were observed at doses above 5mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects. 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 foetus is increased shortly before birth.

6. Pharmaceutical particulars

6.1 List of excipients
Lactose monohydrate (Super Tab 11 SD) USP-NF, Hydroxy propyl cellulose (Klucel EXF) USPNF, Calcium Stearate (Synpro VG) USP-NF, Sodium Carbonate Anhydrous USP-NF, Sodium Lauryl Sulphate (stepanol WA 100) USP-NF, Hypromellose (Methocel E5 LV premium) USP, Ferric oxide, yellow (Sicovit 10E172) USP-

NF, Propylene glycol USP, Titonium dioxide (Kronos 1171) USP, Purified water IHS/USP/Ph.Eur, Methacrylic acid copolymer dispersion (Eudragit L30 D55) USP-NF, Triethyl citrate USP-NF, Polysorbate 80 (Crillet 4) USP-NF.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 Years

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
10's Blister-Alu-Alu pack
3x1 x 10's blister

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements

7. MARKETIN AUTHORISATION HOLDER
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8. Marketing authorisation number(s)

TAN 21 HM 0138

9. Date of first authorisation/renewal of the authorisation

29/03/2021

10. Date of revision of the text

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