SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Pantoprazole 40 mg powder for solution for injection
Pantin

2. Qualitative and quantitative composition
Each vial contains 40 mg of pantoprazole (as sodium).

3. Pharmaceutical form
Injection.

White to off-white lyophilized cake or powder for injection. When constituted as directed, the solution should be a colourless to a light yellow-coloured, clear solution.

4. Clinical particulars

4.1 Therapeutic indications

Gastroesophageal Reflux Disease (GERD) associated with a history of Erosive Esophagitis (EE)
Pantoprazole is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). The safety and efficacy of pantoprazole as a treatment for patients with GERD and a history of EE for more than 10 days have not been demonstrated.

Pathological hypersecretion including Zollinger-Ellison syndrome
Pantoprazole is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) syndrome in adults.

4.2 Posology and method of administration

4.2.1 GERD associated with a history of EE

Dosage
The recommended adult dosage of pantoprazole is 40 mg given once daily by intravenous infusion for 7 to 10 days.

Discontinue treatment with Pantin as soon as the patient is able to receive treatment with pantoprazole sodium delayed-release tablets or oral suspension. Data on the safe and effective dosing for conditions other than those described such as life-threatening upper gastrointestinal bleeds, are not available. Pantin once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

Preparation and method of administration
Only for intravenous infusion (other parenteral routes of administration are not recommended).

Fifteen-minute infusion

- Reconstitute Pantin with 10 mL of 0.9% sodium chloride injection.
- Further dilute with 100 mL of 5% dextrose injection, 0.9% sodium chloride injection, or lactated ringer's injection, to a final concentration of approximately 0.4 mg/mL.
- Inspect the diluted pantoprazole solution visually for particular matter and discolouration prior to and during administration.
- Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Storage

The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light. Do not freeze the reconstituted solution.

Two-minute infusion

- Reconstitute Pantin with 10 mL of 0.9% sodium chloride injection to a final concentration of approximately 4 mg/mL.
- Inspect the diluted pantoprazole solution visually for particular matter and discolouration prior to and during administration.
- Administer intravenously over a period of at least 2 minutes.

Storage

The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light. Do not freeze the reconstituted solution.

4.2.2 Pathological hypersecretion including ZE syndrome

Dosage

The recommended adult dosage of pantoprazole is 80 mg intravenously every 12 hours. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg intravenously every 8 hours is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. The transition from oral to intravenous and from intravenous to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of the effect of suppression of acid secretion. Patients with ZE syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

Preparation and method of administration

Only for intravenous infusion (other parenteral routes of administration are not recommended).

Fifteen-minute infusion

- Reconstitute Pantin with 10 mL of 0.9% sodium chloride injection.

- Combine the contents of the two vials and further dilute with 80 mL of 5% dextrose injection, 0.9% sodium chloride injection, or lactated ringer's injection, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL.
- Inspect the diluted pantoprazole solution visually for particular matter and discolouration prior to and during administration.
- Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Storage

The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light. Do not freeze the reconstituted solution.

Two-minute infusion

- Reconstitute Pantin with 10 mL of 0.9% sodium chloride injection, per vial to a final concentration of approximately 4 mg/mL.
- Inspect the diluted pantoprazole solution visually for particular matter and discolouration prior to and during administration.
- Administer the total volume from both vials intravenously over a period of at least 2 minutes.

Storage

The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light. Do not freeze the reconstituted solution.

Compatibility Information

- Administer pantoprazole intravenously through a dedicated line or a Y-site.
- Flush the intravenous line before and after administration of pantoprazole with either 5% dextrose injection, 0.9% sodium chloride injection or lactated ringer’s injection.
- When administered through a Y-site, pantoprazole is compatible with the following solutions: 5% dextrose injection, 0.9% sodium chloride injection or lactated ringer’s injection.
- Midazolam HCl is incompatible with Y-site administration of pantoprazole.
- Pantoprazole may not be compatible with products containing zinc.
- When pantoprazole is administered through a Y-site, immediately stop using if precipitation or discolouration occurs.

4.3 Contraindications

- Pantoprazole is contraindicated in patients with known hypersensitivity reactions including anaphylaxis to 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 are contraindicated in patients receiving rilpivirine-containing products.

4.4 Special warnings and precautions for use

Presence of gastric malignancy
In adults, symptomatic response to therapy with pantoprazole 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.

Hypersensitivity and severe skin reactions
Anaphylaxis and other serious reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN) have been reported with the use of pantoprazole these may require emergency medical treatment.

Injection site reactions
Thrombophlebitis was associated with the administration of pantoprazole.

Potential for exacerbation of zinc deficiency
Pantoprazole contains edetate disodium (the salt form of EDTA), a chelator of metal ions including zinc. Therefore, zinc supplementation should be considered in patients treated with pantoprazole who are prone to zinc deficiency. Caution should be used when other EDTA-containing products are also co-administered intravenously.

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

***Clostridium difficile*-associated diarrhoea**
Published observational studies suggest that PPI therapy like pantoprazole may be associated with an increased risk of Clostridium difficile-associated diarrhoea, especially in hospitalized patients. This diagnosis should be considered for diarrhoea 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.

Cutaneous and systemic lupus erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole. These events have occurred as both

new onset and an exacerbation of existing autoimmune diseases. 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. The 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 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.

Hepatic effects
Mild, transient transaminase elevations have been observed in clinical studies. The clinical significance of this finding in a large population of subjects administered pantoprazole is unknown.

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 requires 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.

Fundic gland polyposis
PPI use is associated with an increased risk of Fundic gland polyposis that increases with long-term use, especially beyond one year. Most PPI users who developed Fundic gland polyposis 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 tumors
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 tumours. Healthcare providers should temporarily stop pantoprazole 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
Pantoprazole sodium may produce a false-positive urine screen for THC (tetrahydrocannabinol).

Concomitant use of pantoprazole with methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high doses; 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.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with pantoprazole and instructions for preventing or managing them. Consult the labelling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table 1: Clinically relevant interactions affecting drugs co-administered with pantoprazole and interaction with diagnostics

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 • 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. Increased exposure to other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase the 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 is contraindicated. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with pantoprazole 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. A dose adjustment of warfarin may be needed to maintain the target INR range. See prescribing information for warfarin.
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.
Intervention	No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.
Methotrexate	
Clinical Impact	Concomitant use of PPIs with methotrexate (primarily at high doses) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxy methotrexate, 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. 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. and MMF. Use pantoprazole 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 tumours.
Intervention	Temporarily stop pantoprazole 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.

4.6 Pregnancy and lactation

Pregnancy

Reproduction studies have been performed in rats at intravenous pantoprazole doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals and 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 was 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 foetus.

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 as sodium have not been established in paediatric patients.

Animal toxicity data
In a pre-and post-natal development toxicity study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day on postnatal day (PND 4) through PND 21, in addition to lactational exposure through milk. 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 and higher doses. Changes in bone parameters were partially reversible following a recovery period.

In neonatal/juvenile animals (rats and dogs) toxicities were similar to those observed in adult animals, including gastric alterations, decreases in red cell mass, increases in lipids, enzyme induction and hepatocellular hypertrophy. An increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, was observed in the fundic mucosa of stomachs in repeated-dose studies. Full to partial recovery of these effects was noted in animals of both age groups following a recovery period.

Geriatric Use
Of 286 patients in clinical studies of intravenous pantoprazole sodium in patients with GERD and a history of EE, 86 (43%) were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience with oral pantoprazole sodium has not identified differences in responses.

4.7 Effects on the ability to drive and use machines
Pantoprazole has no or negligible influence on the 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 following serious adverse reactions are described below and elsewhere in labelling

- Hypersensitivity and Severe Skin Reactions
- Injection Site Reactions
- Potential for Exacerbation of Zinc Deficiency
- Acute Interstitial Nephritis
- *Clostridium difficile*-associated Diarrhoea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Hepatic Effects
- Hypomagnesemia
- Fundic gland polyposis

Clinical Trials experience

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. Worldwide, approximately 80,500 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment.

Gastroesophageal Reflux Disease (GERD)

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral pantoprazole sodium (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 2.

The number of patients treated in comparative studies with pantoprazole sodium for injection is limited, however, the adverse reactions seen were similar to those seen in the oral studies. Thrombophlebitis was the only new adverse reaction identified with pantoprazole.

Table 2: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%

	Oral pantoprazole sodium (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 oral pantoprazole in US clinical trials with a frequency of ≤2% are listed below by body system:

- Body as a whole: allergic reaction, fever, photosensitivity reaction, facial oedema and thrombophlebitis (I.V. only).
- Gastrointestinal: constipation, dry mouth and hepatitis.
- Hematologic: leukopenia (reported in ex-US clinical trials only), thrombocytopenia
- Metabolic/Nutritional: elevated CPK (Creatine phosphokinase), generalized oedema, elevated triglycerides and liver function test abnormal.
- Musculoskeletal: myalgia.
- Nervous: depression and vertigo.
- Skin and appendages: urticaria, rash and pruritus.
- Special senses: blurred vision.

Zollinger-Ellison (ZE) syndrome
In clinical studies of ZE syndrome, adverse reactions reported in 35 patients administered pantoprazole doses of 80 mg to 240 mg per day for up to 2 years were similar to those reported in adult patients with GERD.

Post-marketing experience
The following adverse reactions have been identified during the post-approval use of pantoprazole sodium tablets and pantoprazole. 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:
General disorders and administration conditions: asthenia, fatigue and malaise.
Immune system disorders: anaphylaxis (including anaphylactic shock) and systemic lupus erythematosus.
Investigations: weight changes.
Skin and subcutaneous tissue disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema (Quincke's oedema) and cutaneous lupus erythematosus.
Musculoskeletal disorders: rhabdomyolysis and bone fracture.
Renal and urinary disorders: interstitial nephritis.
Hepatobiliary disorders: hepatocellular damage leading to jaundice and hepatic failure
Psychiatric disorder: hallucinations, confusion, insomnia and somnolence.
Metabolism and nutritional disorders: hyponatremia and hypomagnesemia.
Infections and infestations: *Clostridium difficile*-associated diarrhoea.
Hematologic: pancytopenia and agranulocytosis.
Nervous: ageusia and dysgeusia.
Gastrointestinal disorders: Fundic gland polyposis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
Experience in patients taking very high doses of pantoprazole (greater than 240 mg) is limited. Adverse reactions seen in spontaneous reports of overdose generally reflect the known safety profile of pantoprazole. Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive. Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) 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
Pharmacological classification: 16.7 Gastric/peptic ulcer medicines.

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 the 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).

Pharmacodynamics effects

Antisecretory activity
The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single doses (20 to 120 mg) of pantoprazole were assessed in a single-dose, open-label, placebo-controlled, dose-response study. The results of this study are shown in Table 3. Healthy subjects received a continuous infusion for 25 hours of pentagastrin (PG) at 1 mcg/kg/h, a dose known to produce submaximal gastric acid secretion. The placebo group showed a sustained, continuous acid output for 25 hours, validating the reliability of the testing model. Pantoprazole had an onset of antisecretory activity within 15 to 30 minutes of administration. Doses of 20 to 80 mg of pantoprazole substantially reduced the 24-hour cumulative PSAO in a dose-dependent manner, despite a short plasma elimination half-life. Complete suppression of PSAO was achieved with 80 mg within approximately 2 hours and no further significant suppression was seen with 120 mg. The duration of action of pantoprazole was 24 hours.

Table 3: Gastric acid output (mEq/hr, mean ± SD) and percent inhibition* (mean ± SD) of pentagastrin-stimulated acid output over 24 hours, following a single dose of pantoprazole i.v. † in healthy subjects.

	2 hours		4 hours		12 hours		24 hours	
Treatment Dose	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition
0 mg (Placebo, n=4)	39±21	NA	26±14	NA	32±20	NA	38±24	NA
20 mg (n=4-6)	13±18	47±27	6±8	83±21	20±20	54±44	30±23	45±43
40 mg (n=8)	5±5	82±11	4±4	90±11	11±10	81±13	16±12	52±36
80 mg (n=8)	0.1±0.2	96±6	0.3±0.4	99±1	2±2	90±7	7±4	63±18

* Compared to individual subject baseline prior to treatment with pantoprazole. NA = not applicable.
† Inhibition of gastric acid output and the percent inhibition of stimulated acid output in response to pantoprazole may be higher after repeated doses.

In one study of gastric pH in healthy subjects, pantoprazole sodium was administered orally (40 mg enteric coated tablets) or pantoprazole sodium for injection (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was the median percent of the time that pH was ≥4 and the results were similar for intravenous and oral medications. However, the clinical significance of this parameter is unknown.

Serum gastrin effects
Serum gastrin concentrations were assessed in two placebo-controlled studies. In a 5-day study of oral pantoprazole with 40 and 60 mg doses in healthy subjects, following the last dose on day 5, median 24-hour serum gastrin concentrations were elevated by 3-to 4-fold compared to placebo in both 40 and 60 mg dose groups. However, by 24 hours following the last dose, median serum gastrin concentrations for both groups returned to normal levels.
In another placebo-controlled, 7-day study of 40 mg intravenous or oral pantoprazole in patients with GERD and a history of EE, the mean serum gastrin concentration increased approximately 50% from baseline and as compared with placebo but remained within the normal range.

During 6 days of repeated administration of pantoprazole injection in patients with ZE syndrome, consistent changes in serum gastrin concentrations from baseline were not observed.

Enterochromaffin-like (ECL) cell effects
There are no data available on the effects of intravenous pantoprazole sodium on ECL cells. In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to oral 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 tumours. Gastric NE-cell tumours 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 oral pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumour without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with oral pantoprazole at 5 mg/kg/day and a 9-month off-dose recovery.

Endocrine effects
In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks did not affect the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, 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 40 mg or 20 mg, there were no changes from baseline in overall levels of T3, T4, and TSH.

Pharmacokinetics
Pantoprazole peak serum concentration (Cmax) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily doses. Following the administration of pantoprazole, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In CYP2C19 extensive metabolizers with normal liver function receiving a 40 mg dose of pantoprazole at a constant rate over 15 minutes, the peak concentration (Cmax) is 5.52 ±1.42 mcg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 ±1.5 mcg hr/mL. The total clearance is 7.6 to 14 L/h.

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.

5.2 Pharmacokinetic properties

Absorption
Pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily doses. Following the administration of pantoprazole, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In CYP2C19 extensive with normal liver function receiving a 40 mg dose of pantoprazole by constant rate over 15 minutes, the peak concentration (C_{max}) is 5.52 ±1.42 mcg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 ±1.5 mcg hr/mL. The total clearance is 7.6 to 14 L/h.

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.

Elimination
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. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Caucasians and African-Americans and 17 to 23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10 hours, they still have minimal accumulation (23% or less) with once-daily dosing.

Excretion
After administration of a single intravenous dose of 14C-labeled pantoprazole sodium to healthy, extensive CYP2C19 metabolizers, 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
After repeated intravenous administration in elderly subjects (65 to 76 years of age), the AUC and elimination half-life values of pantoprazole were similar to those observed in younger subjects.

Male and female patients
After oral administration, there was a modest increase in the AUC and C_{max} of pantoprazole in women compared to men. However, weight-normalized clearance values are similar in women and men.

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 Class A to C), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects when pantoprazole sodium was administered orally. Although serum half-life values increased to 7 to 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. Oral pantoprazole doses higher than 40 mg per day have not been studied in hepatically impaired patients.

5.3 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]), 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 oral 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 a 90% CI of 79 to 93%) when pantoprazole sodium was co-administered 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 micromolar 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 oral 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 C_{max} 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 oral pantoprazole 40 mg per day (n=21). There was a 78% reduction in the C_{max} 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 other 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.

5.4 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 10.0 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, paediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to paediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

Pharmaceutical particulars

6.1 List of excipients
Edetate disodium
Sodium hydroxide
Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
A clear USP type I tubular glass vial, closed with a 20 mm grey bromobutyl rubber stopper and a white flip-off, aluminium seal.

Fill weight: 40 mg.
Pack size: 1 glass vial per carton.

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

6. APPLICANT
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Telangana
India

7. MANUFACTURER

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8. REGISTRATION DETAILS

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