For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

PANSPED I.V.

1. Generic Name

Pantoprazole for injection IP.

2. Qualitative and quantitative Composition:

Each Combipack Contains:

(A) 1 vial of Pantoprazole for injection I.P.

Each vial contains:

Pantoprazole Sodium

(As Lyophilized Powder)

eq. to Pantoprazole ……. 40 mg

(B) 1 Ampoule of Sodium Chloride Injection I.P.

Each ampoule Contains:

Sodium Chloride I.P. ……... 0.9% w/v

Water for injections I.P. ……... q.s. to 10 ml.

3. Dosage form and strength

Dosage form: Injection

Strength: 40 mg

4. Clinical particulars

4.1. Therapeutic indication

PANSPED I.V. is indicated for the treatment of duodenal ulcer, gastric ulcer, moderate and severe reflux oesophagitis.

4.2. Posology and method of administration

Posology

Recommended Dosage for GERD Associated with a History of EE

Adult Patients

The recommended adult dosage of PANSPED I.V. is 40 mg once daily by intravenous injection (over at least 2 minutes) or intravenous infusion (for 15 minutes) for up to 10 days. Discontinue PANSPED I.V. as soon as the patient can tolerate oral treatment. Switch to an appropriate oral medication within 10 days of starting PANSPED I.V.

Paediatric Patients

- The recommended dosage for paediatric patients 3 months of age and older is based on age and actual body weight as shown in Table below.
- Administer as an intravenous infusion over 15 minutes once daily.

Table: Recommended Paediatric Dosage Regimen for GERD and a History of EE

Age and Body Weight		Recommended Dosage Regimen (up to 7 days)
3 months to less than 1 year of age	Less than 12.5 kg	0.8 mg/kg once daily
	12.5 kg and above	10 mg once daily
1 year to 17 years of age	Up to 15 kg	10 mg once daily
	Greater than 15 kg up to 40 kg	20 mg once daily
	Greater than 40 kg	40 mg once daily

• Discontinue PANSPED I.V. as soon as the patient is able to tolerate oral treatment. Switch to an appropriate oral medication within 7 days of starting PANSPED I.V.

Recommended Dosage for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

- The recommended adult dosage of PANSPED I.V. is 80 mg every 12 hours by intravenous injection (over at least 2 minutes) or intravenous infusion (for 15 minutes).
- Adjust the frequency of dosing 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.
- When switching between intravenous to oral formulations of gastric acid inhibitors, consider the pharmacodynamic action of the drugs to ensure continuity of acid suppression.

Preparation and Administration Instructions for GERD Associated with a History of EE

<u>15-Minute Intravenous Infusion for Paediatric or Adult Patients</u>

1. Reconstitute each vial of PANSPED I.V. with 10 mL of 0.9% Sodium Chloride Injection.
2. Dilute the resulting solution to a final concentration as described below:

- Paediatric patients 3 months to less than 1 year of age: Dilute with 21 mL 0.9% Sodium Chloride Injection to a final concentration of approximately 1.3 mg/mL.
- Paediatric patients 1 year to 17 years old and adult patients: Further dilute with 100 mL 5% Dextrose Injection or 0.9% Sodium Chloride Injection to a final concentration of approximately 0.4 mg/mL.

3. Inspect the diluted PANSPED I.V. solution visually for particulate matter and discoloration prior to and during administration.
4. Withdraw the desired dose of the diluted PANSPED I.V. solution for a paediatric or adult dose.
5. Discard any unused portion of the remaining PANSPED I.V. solution.
6. Infuse intravenously over a period of approximately 15 minutes through a dedicated line or through a Y-site.
7. Flush the intravenous line before and after administration of PANSPED I.V. with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

Storage

- Store the reconstituted solution may be up to 6 hours at room temperature up to 30°C (86°F) prior to further dilution.
- Store the diluted solution at room temperature up to 30°C (86°F) and must be used within 24 hours from the time of initial reconstitution.

- Do not freeze the reconstituted or diluted solution.

2-Minute Intravenous Injection for Adult Patients

1. Reconstitute each vial of PANSPED I.V. with 10 mL of 0.9% Sodium Chloride Injection, to a final concentration of approximately 4 mg/mL.
2. Withdraw the dose of 40 mg of reconstituted PANSPED I.V. solution.
3. Inspect the diluted PANSPED I.V. solution visually for particulate matter and discoloration prior to and during administration.
4. Administer intravenously over a period of at least 2 minutes.
5. Flush the intravenous line before and after administration of PANSPED I.V. with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

Storage

- Store the reconstituted solution may be stored for up to 24 hours at room temperature up to 30°C (86°F) prior to intravenous infusion.
- Do not freeze the reconstituted solution.

Preparation and Administration Instructions for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

15-Minute Intravenous Infusion

1. Reconstitute each vial of PANSPED I.V. with 10 mL of 0.9% Sodium Chloride Injection.

2. Combine the contents of the two vials and dilute with 80 mL of 5% Dextrose Injection or Sodium Chloride Injection to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL.

3. Inspect the diluted PANSPED I.V. solution visually for particulate matter and discoloration prior to and during administration.

4. Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

5. Flush the intravenous line before and after administration of PANSPED I.V. with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

Storage

- The reconstituted solution can be stored at room temperature up to 30°C (86°F) for up to 6 hours prior to further dilution.
- Once further diluted, the diluted solution can be stored at room temperature up to 30°C (86°F) for up to 24 hours from the time of initial reconstitution.
- Do not freeze the reconstituted or diluted solution.

2-Minute Intravenous Injection

1. Reconstitute each vial of PANSPED I.V. with 10 mL of 0.9% Sodium Chloride Injection per vial to a final concentration of approximately 4 mg/mL.
2. Inspect the diluted PANSPED I.V. solution visually for particulate matter and discoloration prior to and during administration.
3. Administer the total volume from both vials intravenously over a period of at least 2 minutes.

4. Flush the intravenous line before and after administration of PANSPED I.V. with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

Storage

- The reconstituted solution may be stored for up to 24 hours at room temperature.
- Do not freeze the reconstituted solution.

Compatibility Information

- Administer PANSPED I.V. intravenously through a dedicated line or through a Y-site.
- When administering through a Y-site, PANSPED I.V. is compatible with the following solutions:
    - 5% Dextrose Injection
    - 0.9% Sodium Chloride Injection
- Midazolam hydrochloride is incompatible with Y-site administration of PANSPED I.V. PANSPED I.V. may not be compatible with products containing zinc.
- Stop administering PANSPED I.V. immediately through a Y-site if precipitation or discoloration occurs.

4.3. Contraindications

- PANSPED I.V. 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 tubulointerstitial nephritis, and urticaria.
- Proton pump inhibitors (PPIs), including PANSPED I.V., 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 PANSPED I.V. 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.

Injection Site Reactions

Thrombophlebitis was associated with the administration of PANSPED I.V. Assess the patient and remove the catheter if clinically indicated.

Potential for Exacerbation of Zinc Deficiency

PANSPED I.V. 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 PANSPED I.V. who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were

diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue PANSPED I.V. and evaluate patients with suspected acute TIN.

Clostridioides difficile-Associated Diarrhoea

Published observational studies suggest that PPI therapy like PANSPED I.V. may be associated with an increased risk of Clostridioides 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 guidelines.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs. Discontinue PANSPED I.V. at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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. Most 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. Most 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 PANSPED I.V., 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 PANSPED I.V. is unknown.

Hypomagnesemia and Mineral Metabolism

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. Hypomagnesemia may lead to hypocalcaemia and/or hypokalaemia and may exacerbate underlying hypocalcaemia in at-risk patients. 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.

Consider monitoring magnesium and calcium levels prior to initiation of PANSPED I.V. and periodically while on treatment in patients with a preexisting risk of hypocalcaemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcaemia is refractory to treatment, consider discontinuing the PPI.

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 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 tumors. Healthcare providers should temporarily stop PANSPED I.V. 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 false-positive urine screen for THC (tetrahydrocannabinol).

Concomitant Use of PANSPED I.V. with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate 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. Drugs interactions

Table includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with PANSPED I.V. and instructions for preventing or managing them.

Consult the labelling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table: Clinically Relevant Interactions Affecting Drugs Co-Administered with PANSPED I.V. 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 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 PANSPED I.V. is contraindicated. Nelfinavir: Avoid concomitant use with PANSPED I.V.
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.
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 PANSPED I.V
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 PANSPED I.V. 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 PANSPED I.V. and MMF. Use PANSPED I.V. with caution in transplant patients receiving MMF.
Interactions with Investigations of Neuroendocrine Tumor	
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 PANSPED I.V. 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. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Available data from published observational studies did not demonstrate an association of major malformations or other adverse pregnancy outcomes with pantoprazole.

In animal reproduction studies, no evidence of adverse development outcomes was observed with pantoprazole sodium. Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of harm to the foetus due to pantoprazole in this study.

A pre-and post-natal 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) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. Changes in bone morphology were observed in pups exposed to pantoprazole in utero and through milk during the period of lactation as well as by oral dosing from postnatal day (PND) 4 through PND 21. There were no drug-related findings in maternal animals. Advise pregnant women of the potential risk of foetal harm.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and pantoprazole use. Methodological limitations of these observational studies cannot establish or exclude any drug-associated risk during pregnancy. In a prospective study by the European Network of Teratology Information Services, outcomes from a group of 53 pregnant women administered median daily doses of 40 mg pantoprazole were compared to a control group of 868 pregnant women who did not take any proton pump inhibitors (PPIs). There was no difference in the rate of major malformations between women exposed to PPIs and the control group, corresponding to a Relative Risk (RR)=0.55, [95% Confidence Interval (CI) 0.08–3.95]. In a population-based retrospective cohort study covering all live births in Denmark from 1996 to 2008, there was no significant increase in major birth defects during analysis of first trimester exposure to pantoprazole in 549 live births. A meta-analysis that compared 1,530 pregnant women exposed to PPIs in at least the first trimester with 133,410 unexposed pregnant women showed no

significant increases in risk for congenital malformations or spontaneous abortion with exposure to PPIs (for major malformations OR=1.12 ([95% CI 0.86–1.45] and for spontaneous abortions OR=1.29 [95% CI 0.84–1.97]).

Animal Data

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 foetus due to pantoprazole.

A pre- and post-natal 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.

Lactation

Risk Summary

The limited data from a single case report the presence of pantoprazole in human breast milk. There were no effects on the breastfed infant. There are no data on pantoprazole effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PANSPED I.V. and any potential adverse effects on the breastfed child from pantoprazole or from the underlying maternal condition.

Data

The breast milk of a 42-year-old woman receiving 40 mg of oral pantoprazole, at 10 months postpartum, was studied for 24 hours, to demonstrate low levels of pantoprazole present in the breast milk. Pantoprazole was detectable in milk only 2 and 4 hours after the dose with milk levels of approximately 36 mcg/L and 24 mcg/L, respectively. A milk-to-plasma ratio of 0.022 was observed at 2 hours after drug administration. Pantoprazole was not detectable (<10mcg/L) in milk at 6, 8 and 24 hours after the dose. The relative dose to the infant was estimated to be 7.3 mcg of pantoprazole, which is equivalent to 0.14% of the weight-adjusted maternal dose. No adverse events in the infant were reported by the mother.

Paediatric Use

The safety and effectiveness of PANSPED I.V. for the treatment of GERD and a history of EE for up to 7 days have been established in paediatric patients 3 months of age and older. Use of PANSPED I.V. for this indication is supported by evidence from adequate and well-controlled studies of intravenous and oral pantoprazole sodium in adults and oral pantoprazole sodium in paediatric patients, with additional pharmacokinetic and safety data of intravenous pantoprazole in paediatric patients 1 year of age and older and oral pantoprazole in paediatric patients 3 months of age and older. Adverse reactions were generally similar to those reported in adults with intravenous or oral pantoprazole sodium.

The safety and effectiveness of PANSPED I.V. has not been established in patients less than 3 months of age for the treatment of GERD and a history of EE.

The safety and effectiveness of PANSPED I.V. have not been established in paediatric patients for the treatment of pathological hypersecretory conditions including ZE syndrome.

Animal Toxicity Data

In neonatal/juvenile animals (rats and dogs) toxicities were like 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 were 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 geriatric and younger adult patients, and other reported clinical experience with oral pantoprazole sodium has not identified differences in responses between geriatric and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

No clinically meaningful differences in the pharmacokinetics of pantoprazole were observed in geriatric subjects compared to younger adult subjects.

4.7. Effects on ability to drive and use machines.

Pantoprazole has no or negligible influence on the ability to drive and use machines. However, adverse reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or use machines.

4.8. Undesirable effects

- Injection Site Reactions
- Potential for Exacerbation of Zinc Deficiency
- Acute Tubulointerstitial Nephritis
- Clostridioides difficile-Associated Diarrhoea
- Bone Fracture
- Severe Cutaneous Adverse Reactions
- Cutaneous and Systemic Lupus Erythematosus
- Hepatic Effects
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

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.

Gastroesophageal Reflux Disease (GERD)

Adults

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

The number of patients treated in comparative studies with PANSPED I.V. 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 PANSPED I.V.

Table: 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 sodium 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 edema, thrombophlebitis (intravenous only)

Gastrointestinal: constipation, dry mouth, hepatitis

Hematologic: leukopenia (reported in ex-US clinical trials only), thrombocytopenia

Metabolic/Nutritional: elevated CPK (creatine phosphokinase), generalized edema, elevated triglycerides, liver function tests abnormal.

Musculoskeletal: myalgia

Nervous: depression, vertigo

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Paediatrics:

Adverse reactions reported with single and multiple doses of PANSPED I.V. in 18 hospitalized pediatric patients 1 to 16 years of age were generally like those reported in adults treated with intravenous or oral pantoprazole sodium and in paediatric patients treated with oral

pantoprazole sodium in clinical trials. Additionally, upper respiratory tract infections in paediatric patients less than 16 years of age and otitis media in paediatric patients less than 1 year of age were reported with oral pantoprazole sodium.

Zollinger-Ellison (ZE) Syndrome:

In clinical studies of ZE Syndrome, adverse reactions reported in 35 patients administered PANSPED I.V. 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 post approval use of pantoprazole sodium products. 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, malaise

Immune system disorders: anaphylaxis (including anaphylactic shock), systemic lupus erythematosus.

Investigations: weight changes

Skin and subcutaneous tissue disorders: severe dermatologic reactions (some fatal), including erythema multiforme, SJS/TEN, DRESS, AGEP, angioedema (Quincke's edema) and cutaneous lupus erythematosus.

Musculoskeletal disorders: rhabdomyolysis, bone fracture

Renal and genitourinary disorders: acute tubulointerstitial nephritis, erectile dysfunction

Hepatobiliary disorders: hepatocellular damage leading to jaundice and hepatic failure.

Psychiatric disorder: hallucinations, confusion, insomnia, somnolence

Metabolism and nutritional disorders: hyponatremia, hypomagnesemia, hypocalacemia, hypokalaemia

Infections and infestations: Clostridioides difficile-associated diarrhoea

Hematologic: pancytopenia, agranulocytosis

Nervous: ageusia, dysgeusia

Gastrointestinal disorders: fundic gland polyps

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

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 haemodialysis. 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. 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. Pharmacodynamic properties

Antisecretory Activity

The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single doses (20 to 120 mg) of PANSPED I.V. were assessed in a single-dose, open-label, placebo-controlled, dose-response study. The results of this study are shown in Table 4. 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. PANSPED I.V. had an onset of antisecretory activity within 15 to 30 minutes of administration. Doses of 20 to 80 mg of PANSPED I.V. 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 PANSPED I.V. was 24 hours.

Table: 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 PANSPED 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

NA = not applicable

[*] Compared to individual subject baseline prior to treatment with PANSPED I.V

† Inhibition of gastric acid output and the percent inhibition of stimulated acid output in response to PANSPED I.V. may be higher after repeated doses.

In one study of gastric pH in healthy subjects, pantoprazole was administered orally (40 mg enteric coated tablets) or PANSPED I.V. (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was median percent of 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 PANSPED I.V. in patients with ZE Syndrome, consistent changes of 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 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 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 had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T), thyroxine (T), 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 T, T, and TSH.

5.3. Pharmacokinetic properties

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 dosing. Following the administration of PANSPED I.V., 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 PANSPED I.V. 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

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. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Whites 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 C-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.

Pediatric Patients

The pharmacokinetics of pantoprazole were studied in 40 pediatric patients 1 to less than 16 years of age in three open-label clinical trials in pediatric patients with GERD following intravenous administration and 180 pediatric patients from birth to 16 years of age in four randomized, open-label clinical studies in pediatric patients with GERD following oral administration.

Population PK analyses predicted the following dosage regimens would achieve comparable steady-state plasma exposures (AUC) to those observed in adult patients administered 40 mg of PANSPED I.V. once daily: 0.8 mg/kg once daily for pediatric patients 3 months to less than 1 year, 10 mg once daily for pediatric patients 1 year to 17 years with body weight less than 15 kg, 20 mg once daily for pediatric patients 1 year to 17 years with body weight greater than 15 kg but less than 40 kg, and 40 mg once daily for pediatric patients 1 year to 17 years with body weight of 40 kg and greater. The pharmacokinetics of pantoprazole following intravenous administration in pediatric patients less than 3 months of age have not been characterized.

Male and Female Patients

After oral administration there was a modest increase in the AUC and C 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.

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 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 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 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 (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**.**

6. Nonclinical particulars

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with pantoprazole doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment with 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment with 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with pantoprazole doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment with 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with pantoprazole doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment with 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment with 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

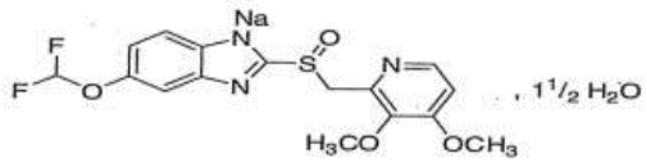
Pantoprazole was positive in the in vitro human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the in vitro Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results

were observed in the in vivo rat liver DNA covalent binding assay. Pantoprazole was negative in the in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the in vitro AS52/GPT mammalian cell-forward gene mutation assay, the in vitro thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the in vivo rat bone marrow cell chromosomal aberration assay.

There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

7. Description

Pantoprazole Sodium is sodium 5-(difluromethoxy)- 2[[(3,4-dimethoxy-pyridin-2-yl)methyl]sulphinyl]-benzimidazol-1-ide,sesquihydrate. The empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$, and its molecular weight is 432.4 g/mol. The chemical structure of Pantoprazole Sodium is:



Pansped I.V.

Pantoprazole for injection is white or almost white Powder filled in amber colour glass vial sealed with rani red colour flip off seal.

8. Pharmaceutical particulars

8.1. Incompatibilities

None stated

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

PANSPED I.V. is available in 10 mL moulded amber glass vial USP Type III.

8.4. Storage and handing instructions.

Store below 25^{o}C. Protect from light & Moisture. Do not Freeze.

Keep medicine out of reach of children.

The Constituted solution should be used immediately after preparation.

If any particle is visible in the vial after dissolving the contents please do not use the solution.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.

- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Pure & Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No. 26A, 27-30, Sector -8A,

I.I.E., SIDCUL, Ranipur,

Haridwar-249 403, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No. is 51/UA/SC/P-2013, issue on 09.05.2024.

12. Date of revision

NA

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