Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Pantoprazole for Injection BP

(Brand Name: P-PPi ® Injection)

2. Qualitative and Quantitative Composition

Each Combipack Contains:

a) One vial of Pantoprazole for Injection BP 40 mg

Each vial contains:

Pantoprazole Sodium (Sterile) (As Lyophilized Bulk) Equivalent to Pantoprazole …..… 40 mg.

b) One 10 ml ampoule (FFS) of Sodium Chloride Injection IP …...…… 0.9% w/v.

3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Pantoprazole 40 mg per vial.

4. Clinical Particulars

4.1 Therapeutic Indication

P-PPi injection is indicated in the following:

- Gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis.
- Gastric and duodenal ulcer.
- Zollinger-Ellison Syndrome and other pathological hypersecretory conditions.

4.2Posology and Method of Administration

To be administered only by intravenous (I.V.) route in adults.

Pantoprazole I.V. injection is recommended only if oral administration is not appropriate. Data on I.V. use of pantoprazole is available for up to 7 days. Therefore, as soon as oral therapy is possible, treatment with pantoprazole I.V. injection should be discontinued and oral therapy should be administered instead.

- **Treatment of gastric and duodenal ulcer, reflux/erosive esophagitis, and GERD:** The recommended dose of pantoprazole is 40 mg once daily for 7 to 10 days.
- **Management of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions:** Initiate treatment with a daily dose of 80 mg pantoprazole. Thereafter, the dosage can be titrated up or down as needed. Whenever daily dose requirement is above 80 mg, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for

adequate acid control. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. Transition from oral to I.V. and from I.V. to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion.

Or, as prescribed by the Physician.

Directions for Reconstitution and Dilution

A ready-to-use solution is prepared by injecting 10 ml of 0.9% sodium chloride injection (provided separately as a part of combipack) into the vial containing pantoprazole 40 mg powder for solution for injection. Shake vial thoroughly to form solution. The appearance of the product after reconstitution is a colourless to faintly yellow solution. This solution may be administered directly or may be administered after mixing it with 100 ml of compatible diluents. The reconstituted solution should be administered by I.V. bolus over a period of at least 2 minutes. The reconstituted and diluted solution should be administered by I.V. infusion over a period of 15 minutes.

Compatible Diluents for I.V. Infusion Use

- Lactated Ringer's Injection.
- 0.9% Sodium Chloride Injection.
- 5% Dextrose Injection.

Pharmaceutical Precautions

The vials are for single use only. The reconstituted/diluted solution should be used immediately after preparation. Do not freeze. Unused portion of solution, if any, should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit. Do not use if reconstituted solution is cloudy or discolored or contains visible particles. The diluted solution should not be used if crystals or precipitates are observed.

4.3Contraindications

P-PPi Injection is contraindicated in patients with known hypersensitivity to pantoprazole, or to any substituted benzimidazoles, or to any component of the formulation.

4.4Special Warnings and Precautions for Use

Test dose: Before therapy with P-PPi Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to the ingredients of P-PPi Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

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 use of I.V. pantoprazole. These may require emergency medical treatment.

Injection site reactions: Thrombophlebitis has been associated with the administration of I.V. pantoprazole.

Gastric malignancy: Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. In the presence of alarming symptoms (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anemia or melena) and when gastric ulcer is suspected or present, malignancy should be excluded. Further investigation is to be considered if symptoms persist despite adequate treatment.

Hepatic impairment: In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued.

Gastrointestinal infections caused by bacteria: Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole injection may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

***Clostridium difficile*-associated diarrhea (CDAD):** Published observational studies suggest that PPI therapy may be associated with an increased risk of CDAD, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hypomagnesaemia: Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g., diuretics), it is advisable to measure magnesium levels before starting PPI treatment and periodically during treatment.

Bone fractures: PPIs, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognized risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture by 10 to 40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE): PPIs are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional

should consider stopping pantoprazole injection. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

4.5Drug Interactions

Drugs with pH-dependent absorption: Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral bioavailability e.g., some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib, ampicillin esters, iron salts, and digoxin.

Co-administration with HIV protease inhibitors: Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir or nelfinavir, due to significant reduction in their bioavailability. If the combination of HIV protease inhibitors with a PPI is judged unavoidable, close clinical monitoring (e.g., virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin): Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or international normalised ratio (INR - measurement of how long it takes blood to form a clot). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate: Concomitant use of high dose methotrexate (e.g., 300 mg) and PPIs has been reported to increase methotrexate levels in some patients. Therefore, in settings where high-dose methotrexate is used (e.g., cancer and psoriasis), a temporary withdrawal of pantoprazole may need to be considered.

Drugs that inhibit or induce CYP2C19: Inhibitors of CYP2C19, such as fluvoxamine, could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4, such as rifampicin and St John´s wort (Hypericum perforatum), may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

Antacids: There were no interactions with concomitantly administered antacids.

Clopidogrel: Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effects on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole injection.

Antibiotics: Interaction studies have also been performed by concomitantly administering pantoprazole with common antibiotics (clarithromycin, metronidazole, amoxicillin) used in the

treatment of peptic ulcer disease caused by *Helicobacter pylori* bacteria. No clinically relevant interactions were found.

Drugs metabolized by cytochrome P450 enzyme: Pantoprazole is extensively metabolized in the liver via the cytochrome P450 (CYP) enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4. Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with P-glycoprotein related absorption of digoxin. An interaction of pantoprazole with other drugs metabolized using the same enzyme system cannot be excluded.

Interference with Laboratory Tests

Chromogranin A (CgA) test: During treatment with antisecretory drugs like pantoprazole, CgA (protein found in carcinoid tumor cells) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole injection treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, tests should be repeated 14 days after cessation of PPI treatment.

False positive urine tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including pantoprazole. An alternative confirmatory method should be considered to verify positive results.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Animal studies have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole injection. However, there are no adequate and well-controlled studies available for use of pantoprazole injection in pregnant women. The potential risk for humans is unknown. Because animal reproduction studies are not always predictive of human response, pantoprazole injection should be used during pregnancy only if clearly needed.

Lactating Women

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to the mother.

Pediatric Patients

The experience in children is limited. The safety and efficacy of pantoprazole injection in children below 18 years of age have not been established. Therefore, pantoprazole injection is not recommended for use in patients below 18 years of age.

Geriatric Patients

After repeated I.V. administration in elderly subjects (65 to 76 years of age), pharmacokinetic parameters of pantoprazole were similar to those observed in younger subjects. No dosage adjustment is recommended for elderly patients.

Renal Impairment Patients

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment Patients

No dosage adjustment is needed in patients with mild to moderate hepatic impairment. However, in patients with severe liver impairment, a daily dose of 20 mg pantoprazole should not be exceeded. Doses higher than 40 mg/day have not been studied in these patients.

4.7Effect on 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.

4.8Undesirable Effects

Clinical Trials Experience

Adverse reactions reported with oral pantoprazole in clinical trials of adult patients with GERD at a frequency of >2% were as follows:

Headache 12.2%, diarrhea 8.8%, nausea 7.0%, abdominal pain 6.2%, vomiting 4.3%, flatulence 3.9%, dizziness 3.0%, and arthralgia 2.8%.

A limited number of patients were treated in comparative studies with I.V. pantoprazole; however, the adverse reactions were similar to those seen in the oral studies.

Additional adverse reactions that were reported with a frequency of ≤ 2% are listed below by body system:

- Body as a Whole: Allergic reaction, fever, photosensitivity reaction, facial edema, thrombophlebitis (I.V. only).
- Gastrointestinal: Constipation, dry mouth, hepatitis.
- Hematologic: Leukopenia, thrombocytopenia.
- Metabolic/Nutritional: Elevated CPK (creatine phosphokinase), generalized edema, elevated triglycerides, abnormal liver function tests.

- Musculoskeletal: Myalgia.
- Nervous: Depression, vertigo.
- Skin and Appendages: Urticaria, rash, pruritus.
- Special Senses: Blurred vision.

Post-marketing Experience

Acute kidney injury as an adverse drug reaction reported with the use of PPIs. The following adverse reactions have been identified during post-approval use of pantoprazole injection. 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).
- Investigations: Weight changes.
- Skin and Subcutaneous Tissue Disorders: Severe dermatologic reactions (some might be fatal), including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), and angioedema (Quincke's edema).
- Musculoskeletal Disorders: Rhabdomyolysis, fractures.
- Renal and Urinary Disorders: Interstitial nephritis.
- Hepatobiliary Disorders: Hepatocellular damage leading to jaundice and hepatic failure.
- Psychiatric Disorder: Hallucinations, confusion, insomnia, somnolence.
- Metabolism and Nutritional Disorders: Hyponatremia, hypomagnesaemia.
- Infections and Infestations: *Clostridium difficile*-associated diarrhea.
- Hematologic: Pancytopenia, agranulocytosis.
- Nervous: Ageusia, dysgeusia.

4.9 Overdose

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Adverse events seen in spontaneous reports of overdose generally reflect the known safety profile of pantoprazole. There are no known symptoms of overdose in humans. The symptoms of acute toxicity reported in animal studies were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

As pantoprazole is extensively protein bound, it is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

5. Pharmacological Properties

5.1 Mechanism of Action

Pantoprazole is a substituted benzimidazole derivative of proton pump inhibitor (PPI). Pantoprazole is converted to its active form in the acidic environment of the gastric parietal cells. Pantoprazole suppresses the final step in the production of gastric acid (hydrochloric acid - HCl) by covalently binding to the H+, K+-ATPase enzyme system (also referred as proton pump) at the secretory surface of the parietal cells in the stomach. This effect leads to dose dependent inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the H+, K+-ATPase results in duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 to 120 mg).

5.2Pharmacodynamic Properties

1. Antisecretory Activity and Effect on Gastrin

As with other PPIs and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

2. Serum Gastrin and Enterochromaffin-Like (ECL) Cell Effects

The fasting gastrin values increase under pantoprazole therapy. On short-term use, in most cases, they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine cells (ECL) in the stomach is observed in a minority of cases during long-term treatment (similar to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments have not been observed in humans.

5.3Pharmacokinetic Properties

Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, kinetics of pantoprazole are linear after both oral and I.V. administration.

Absorption: Pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to I.V. doses from 10 to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

Distribution: The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 liters, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism: Pantoprazole is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4.
Excretion: Terminal half-life of pantoprazole is about 1 hour. Because of specific binding of pantoprazole to the proton pumps of the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion). Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest are excreted in the faeces. The main metabolite in both the serum and urine is desmethyl pantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

6. Nonclinical Properties

6.1 Animal Toxicology

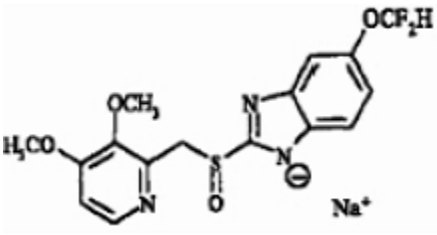
Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the fore-stomach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

7. Description

P-PPi Injection is white to off white lyophilized powder filled in 10 ml clear color glass vials.

Pantoprazole is proton pump inhibitor (PPI) drug which inhibits gastric acid secretion. Pantoprazole sodium is a white to off-white crystalline powder and is racemic mixture. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH.
Molecular Weight: 405.4 g/mol.
Molecular Formula: C16H14F2N3NaO4S.

Chemical Name: Sodium;5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl] benzimidazol-1-ide.
Structural Formula:



8. Pharmaceutical Particulars

8.1 Incompatibilities

Midazolam hydrochloride has been shown to be incompatible with pantoprazole injection.
P-PPi Injection should not be mixed with any other solution/injection for which physical and chemical compatibility has not been established.

8.2Shelf-life

Unopened vial (powder): 24 months.
Opened vial: After reconstitution or, reconstitution and dilution, the solution is stable for 12 hours at 25°C. However, to avoid microbiological contamination, the solution should be used immediately. Unused portion of the solution, if any, should be discarded.

8.3Packaging Information

Combipack of one glass vial of drug powder and one ampoule (10 ml) of sodium chloride injection for reconstitution.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 25°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patient to store medication as advised and not to expose the vial to moisture or direct light.
- Instruct patient not to freeze the reconstituted solution and use it immediately after the preparation. Unused portion of solution, if any, should be discarded.
- Instruct patients not to use if solution is cloudy or discolored or contains visible particles. The diluted solution should not be used if crystals or precipitates are observed.

- Instruct patients to stop medicine immediately and inform their healthcare professionals if they develop any allergic/hypersensitivity reactions.
- Instruct patients to inform their healthcare provider if they are currently taking any other medications, including over-the-counter (OTC) medications or if they are allergic to any medications.

10.Details of Manufacturer

Aqua Vitoe Laboratories,
Plot No 4, Vill. Kunjhal, Near Jharmajri,
Baddi, Distt. Solan – 173205 (H.P.), India.

11. Details of Permission or License Number with Date

Manufacturing license No. MB/07/536 dated 02/03/2018.

12. Date of Revision

September 2022.

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