For the use of a Registered Medical Practitioner only

[Rx] Pantoprazole for Injection BP 40 mg

Panum® IV 40

(Combipack with Sodium Chloride Injection IP 0.9% w/v)

COMPOSITION:

Each vial contains:

Pantoprazole Sodium IP

(As sterile Lyophilized bulk)

equivalent to Pantoprazole ..... 40 mg

10 ml Sodium Chloride Injection IP

Each FFS ampoule contains:

Sodium Chloride IP ..... 0.9% w/v

Water for Injections IP ..... q.s.

DOSAGE FORM AND STRENGTH

Powder for Injection

THRERAPEUTIC INDICATIONS

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

PSOLOGY AND METHOD OF ADMINISTRATION

Duodenal ulcer, gastric ulcer, moderate and severe reflux oesophagitis:

The recommended adult dosage of Panum I.V. is 40 mg given once daily.

The intravenous administration is recommended only in cases where the oral administration is not indicated. As soon as oral therapy is possible the intravenous therapy should be discontinued.

Inspect the solution visually for particular matter and discoloration prior to and during administration.

Method of administration

The solution is to be inspected visually for particulate matter and discolouration prior to administration and should only be used if it is clear and free from particles.

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

Fifteen Minute Infusion

Pantoprazole I.V. for injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, BP, and further diluted (admixed) with 100 mL of 5% Dextrose Injection, BP, 0.9% Sodium Chloride Injection, IP, or Lactated Ringer's Injection, IP, to a final concentration of approximately 0.4 mg/mL. The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. Pantoprazole I.V. for injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Two- Minute Infusion

Pantoprazole I.V. for injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, IP, to a final concentration of approximately 4 mg/mL. The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion. Pantoprazole I.V. for injection should be administered intravenously over a period of at least 2 minutes.

CONTRAINDICATIONS

- Pantoprazole 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 interstitial nephritis, and urticaria.
- Proton pump inhibitors (PPIs), including Pantoprazole I.V., are contraindicated in patients receiving rilpivirine-containing products.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with Pantoprazole 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.

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 Pantoprazole I.V. These may require emergency medical treatment.

Injection Site Reactions

Thrombophlebitis was associated with the administration of Pantoprazole I.V.

Potential for Exacerbation of Zinc Deficiency

Pantoprazole 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 Pantoprazole I.V. 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 I.V. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Pantoprazole I.V. if acute interstitial nephritis develops.

Clostridium difficile-Associated Diarrhea

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

Bone Fracture

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

Cutaneous and Systemic Lupus Erythematosus

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

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

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

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Pantoprazole 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 Pantoprazole I.V. 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 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

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 Pantoprazole 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 Pantoprazole I.V. with Methotrexate

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

DRUG INTERACTIONS

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

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

Antiretrovirals

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.

Rilpivirine-containing products: Concomitant use with Pantoprazole I.V. is contraindicated.

Atazanavir: See prescribing information for atazanavir for dosing information.

Nelfinavir: Avoid concomitant use with Pantoprazole I.V. See prescribing information for nelfinavir.

Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.

Other antiretrovirals: See prescribing information.

Warfarin

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.

Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.

Clopidogrel

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.

No dose adjustment of clopidogrel is necessary when administered with an approved dose of Pantoprazole I.V.

Methotrexate

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.

A temporary withdrawal of Pantoprazole 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)

Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

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 I.V. and MMF. Use Pantoprazole I.V. 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

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.

Temporarily stop Pantoprazole 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

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.

An alternative confirmatory method should be considered to verify positive results.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Pregnancy Category C

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

Nursing Mothers

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

Pediatric Use

The safety and effectiveness of Pantoprazole I.V. have not been established in pediatric patients.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly (65 years and above) and younger subjects, and other reported clinical experience with oral pantoprazole sodium has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

UNDESIRABLE EFFECTS

Proton Pump Inhibitors associated Acute Kidney Injury: Acute kidney injury has been reported with the use of Proton pump inhibitors (PPIs) including Pantoprazole, Omeprazole, lansoperazole, Esomeprazole, Rabeprazole etc.

Body as a Whole: allergic reaction, fever, photosensitivity reaction, facial edema, thrombophlebitis (I.V. only)

Gastrointestinal: constipation, dry mouth, hepatitis, diarrhea, nausea, vomiting, abdominal pain, flatulence

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, arthralgia

Nervous: depression, vertigo, headache, dizziness

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Post-marketing experience:

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, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema (Quincke's edema) and cutaneous lupus erythematosus

Musculoskeletal Disorders: rhabdomyolysis, bone fracture

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, hypomagnesemia

Infections and Infestations: Clostridium difficile associated diarrhea

Hematologic: pancytopenia, agranulocytosis

Nervous: ageusia, dysgeusia

Gastrointestinal Disorders: fundic gland polyps

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, Proton pump inhibitors.

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 anti-secretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Pharmacokinetic properties

Absorption

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 dosing. Following the administration of Pantoprazole 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 Pantoprazole I.V. by 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.

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 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 Cmax 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 coadministered with clopidogrel as compared to clopidogrel administered alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 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 Cmax and 27% reduction in the AUC of MPA. Transplant patients receiving approximately 2000 mg per day of MMF (n=12) were compared to transplant patients receiving approximately the same dose of MMF and oral pantoprazole 40 mg per day (n=21). There was a 78% reduction in the Cmax and a 45% reduction in the AUC of MPA in patients receiving both pantoprazole and MMF.

Other Drugs

In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of 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.

DESCRIPTION

The active ingredient in Panum IV for Injection is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl] 1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$, with a molecular weight of 405.4.

INCOMPATABILITIES

- Administer Pantoprazole I.V. intravenously through a dedicated line or through a Y-site.
- Flush the intravenous line before and after administration of Pantoprazole I.V. with either 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection.
- When administered through a Y-site, Pantoprazole I.V. is compatible with the following solutions: 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection.
- Midazolam HCl has been shown to be incompatible with Y-site administration of Pantoprazole I.V.
- Pantoprazole I.V. may not be compatible with products containing zinc
- When Pantoprazole I.V. is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.

STORAGE AND HANDLING INSTRUCTIONS

Store below 25°C. Protect from light.

PACKAGING INFORMATION

Vial of 10 ml with 10 ml Sodium Chloride Injection IP

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

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Note: This prescribing information is applicable for India Market only.