For the use of a Registered Medical Practitioner only

℞ Pantoprazole Sodium & Sustained Release Levosulpiride Capsules

Panum® L

COMPOSITION

Each hard gelatin capsule contains:
Pantoprazole Sodium IP
eq. to Pantoprazole ..... 40 mg
(as enteric coated pellets)
Levosulpiride ..... 75 mg
(as sustained release pellets)
Colour: Brilliant Blue FCF
Approved colours used in capsule shells.

PHARMACEUTICALFORM

Hard gelatin capsule

THERAPEUTIC INDICATION

For short term treatment of GERO in adult patients who do not respond to PPI alone.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 tablet once daily or as directed by the Physician.

Method of administration: For oral use.

The Pantoprazole and Levosulpiride capsule should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

CONTRAINDICATIONS

Contraindicated if hypersensitivity to the pantoprazole, levosulpiride or any other excipients of the formulation.

Pheochromocytoma as it can cause hypertensive attack probably due to release of catecholamine from tumor: such attacks can be controlled with phentolamine.

Epilepsy, manic states such as in the manic phase of manic depressive psychosis. Concomitant prolactin dependent tumors like pituitary gland prolactinomas and breast cancer.

Use of Pantoprazole and sustained release levosulpiride capsule is contraindicated during pregnancy and lactation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients of gastric term with pantoprazole, particularly in patients who were H. Pylori positive.

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

Published observational studies suggest that PPI therapy like pantoprazole 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.

Several published observational studies suggest that proton pump inhibitor (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.

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPls for at least three months, 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 PPls with medications such as digoxin or drug that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Due to the chronic nature of GERO, there may be a potential for prolonged administration o pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and cause rare types of gastrointestinaltumors. The relevance of these findings to tumor development in humans is unknown.

Literature suggests that concomitant use of PPls with methotrexate (primarily at high dose) 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.

In a clinical pharmacology study, pantoprazole delayed release 40mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, trilodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, rennin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1-year study of GERO patients treated with pantoprazole delayed release 40 mg or 20 mg, three were no changes from baseline in overall levels of T3, T4 and TSH.

Caution is advised when the drug is administered to patients with cerebrovascular events including risk factor for stroke. Caution is also advised when levosulpiride is given to patients with cardiac insufficiency.

Levosulpiride should not be used when gastrointestinal stimulation of motility can be harmful, e.g., in presence of gastrointestinal hemorrhage, mechanical obstructions or perforations.

Levosulpiride may cause drowsiness in some patients, especially at higher doses, thus patients should be advised to exercise caution when driving or operation machinery.

DRUG INTERACTION

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or neltinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance. There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with absorption of drug where gastric PH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors. An alternative confirmatory method should be considered to verify positive results.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPls and methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPls have been conducted.

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.

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 75mg per day) aloe and with pantoprazole (80mg at the same time as clopidogrel) for 5 days. On day 5, the mean AUC of the active metabolite ofclopid ogre l was reduced by approximately 14% (geometric mean ration was 86% with 90% Cl of 79 to 93%) when pantoprazole 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 um ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, dsmethyldiazepam), diclofenac, naproxen piroxicam, digoxin, ethanol, glyburide an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, oramoxicillin. There was also no interaction with concomitantly administered antacids.

Caution is advised when levosulpiride is taken concomitantly with other centrally acting drugs. It can potentiate the cognitive and motor effects of alcohol.

The effect of levosulpiride on gastrointestinal motility can be antagonized by anti-cholinergic drugs, narcotics and analgesic drugs.

USE IN SPECIAL POPULATION

Elderly: No dose adjustment of pantoprazole is necessary in older people.

The dosage of levosulpiride should be decided by the physician which must carefully evaluate a possible reduction of the dosages according to age-related clinical parameters.

Paediatric population: Pantoprazole is not recommended for use in children <12 years of age because of limited data on safety and efficacy in the age group.

No data are available for levosulpiride in Paediatrics.

Patients with hepatic impairment: A daily dose of 20mg pantoprazole (1 tablet of 20mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole must not be used in combination treatment for eradication of H. pylori in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment of these patients. In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long term use.

Patients with renal impairment: Nodose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). Pantoprazole must not be used in combination treatment for eradication of H. pylori in patients with impaired renal function since currently no data are available on the efficacy and safety of Pantoprazole in combination treatment for these patients.

Pregnancy: A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feta/neonatal toxicity of Pantoprazole. Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Pantoprazole during pregnancy.

Do not use levosulpiride in pregnancy, possible pregnancy and during the breast feeding period. Neonates exposed to conventional or atypical antipsychotics included Product name during the third trimester of pregnancy are at risk for side effects including extrapyramidal symptoms or withdrawal symptoms that may vary by severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder. Therefore, newborns should be carefully monitored.

Breast-feeding: There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from Pantoprazole therapy taking into account the benefit of breast-feeding for the child, and the benefit of Pantoprazole therapy for the woman.

Fertility: There was no evidence of impaired fertility following the administration of pantoprazole in animal studies .

EFFECTS ON ABILIT Y 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.

Levosulpiride has major influence on the ability to drive and use machines. High doses of levosulpiride may cause drowsiness, numbness, or dyskinesias, therefore they should be advised to avoid driving and operations requiring supervision.

ADVERSE DRUG REACTIONS / 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, Lansoprazole, Esomeprazole, Rabeprazole etc.

The most frequently occurring adverse reactions, occurring at a rate of >2%, inpatients on oral pantoprazole (20mg or 40 mg) were headache, diarrhea, nausea, abdominal pain, vomiting flatulence, dizziness and arthralgia. Additional adverse reaction that were reported for pantoprazole with a frequency of <2% were allergic reaction, pyrexia, photosensitivity reaction, facial edema, constipation, dry, mouth hepatitis, leucopenia, thrombocytopenia, elevated CK (creatine kinese) generalized edema, elevated triglycerides, elevated liver enzymes, myatgia, depression , vertigo, urticaria, rashpruitus and blurred vision.

In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions included URI, Headache, fever, diarrhea, vomiting, rash and abdominal pain. Additional adverse reactions reported for pantoprazole in pediatric patients with frequency of <4% were allergic reaction, facial edema, constipation, flatulence, nausea, elevated triglycerides, elevated liver enzymes, elevated CK (creatine kinase), arthralgia, myalgia, dizziness, vertigo and urticaria. Adverse reactions not reported in pediatric patients but are considered relevant to pediatric patients are photosensitivity reaction dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leucopenia, and blurred vision.

Adverse reactions identified during post approval use of pantoprazole were asthenia, fatigue, malaise, pancytopenia, agranulocytosis, anaphylaxis (including anaphylactic shock), clostridium difficile associated diarrhea, weight changes, hyponatremia, hypomagnesemia, severe dermatologic reactions (some fatal), including erythema multiforme, stevens-johnsons syndrome, and toxic epidermal necrolysis (TEN, some fatal), and angioedema (Quincke's edema), rhabdonmyolysis, bone fracture, ageusia dysgeusiaa interstitial nephritis, hepatocellular demage leading to jaundice and hepatic failure, hallucination and confusion, insomnia, and somnolence.

With prolonged administration of levesulpiride, disturbances such as amenorrhea, gynecomastia, glactrorrhea, hyperprolactinemia and changes in libido are observed: in particular cases, reversible effects of levosulpiride on functioning of hypothalamic pituitary gonadal axis are observed.

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@jbpharma.com

OVERDOSE

There are no known symptoms of pantoprazole overdose in man. Systemic exposure with up to 240 mg administered intravenously over 2 minutes were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. Single oral doses of pantoprazole at 709mg/kg, 798mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

Normal therapeutic dose of levosulpiride, the range the possibility of side effects are less. But extrapyramidal disturbances and sleep disorders may occur with-higher doses and in patients who are sensitive to dopamine antagonists. In such cases therapy should be stopped or the dose should be reduced as dictated by the clinical condition of the patient.

PHARMACOLOGICALPROPERTIES

Pantoprazole, is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+ ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. As with other proton pump inhibitors 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.

Levosulpiride, is the levorotatory enantiomer of sulpiride, a substituted benzamide derivative. It is a selective DA2 receptor blocker at proximal gastrointestinal tract and at the chemoreceptor trigger zone (CTZ). Levosulpiride selectively blocks DA2 receptors at the central level and at the sumucosal and myenteric plexus peripheral level, which interacts with the chlingeric, adrenergic and peptidergic fibres to regulate the motility of gastrointestinal tract (GIT). Dopamine inhibits the cholinergic neurons of the upper gastrointestinal tract, and levosulpiride acts as a prokinetic agent blocking the inhibition and hence permitting a sustained cholinergic induced contraction of smooth muscle cell in the myenteric plexus. Via its antagonistic actions on the dopamine receptor in the CTZ, it display a strong antiemetic effect.

PHARMACOKINETIC PROPERTIES

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. The absolute bioavailability from the tablet was found to be about 77%.

The bioavailability of levosulpiride, when given orally is low (about 27% to 34%) with incomplete absorption as opposed to pre-systemic metabolism. Food reduces absorption by 30%.

Distribution

Pantoprazol'es serum protein binding is about9 8%. Volume of distribution is about 0.15I/kg.

Levosulpiride displays a protein binding of about 14% and volume of distribution of 1 to 2.7 Ukg which is similar in elderly and younger subjects.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (GYP) system.

Levosulpiride, the lack of hepatic metabolism makes metabolic interactions with cytochrome P-450 related substances very unlikely.

Excretion

Renal elimination represents the major route of excretion (about BO%) for the metabolites of pantoprazole, the rest is excreted with the faeces.

Metabolism of levosulpiride does not occur and the drug is excreted unchanged into the urine. The renal clearance is 15 to 30%. The drug is substantially excreted in the feces due to poor absorption.

INCO MPATIBI LITY

Not applicable.

STORAGE INSTRUCTIONS

Store protected from light & moisture, at a temperature not exceeding 30°C. Keep out of reach of children.

PACKAGING INFORMATION

Blister of 10 Capsules

Marketed by :
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