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

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

Prescribing Information

1. Generic Name

Pantoprazole (GR) and Levosulpiride (SR) Capsules
(Brand Name: P-PPi®-L Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Pantoprazole Sodium IP equivalent to Pantoprazole ……..... 40 mg
(as Gastro-resistant tablet)
Colours: Tartrazine & Titanium Dioxide IP.
Levosulpiride ……..…… 75 mg
(as uncoated sustained release tablet)
Excipients …… q.s.
Colours used in capsule shell : Brilliant Blue FCF, Erythrosine, Titanium Dioxide IP.
Methylparaben and Propylparaben used as Antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Pantoprazole 40 mg (in gastro-resistant form) with levosulpiride 75 mg (in sustained release form) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

P-PPi-L Capsules are indicated for the treatment of gastro-esophageal reflux disease (GERD) in patients who do not respond to PPI (proton-pump inhibitor) alone.

4.2Posology and Method of Administration

<u>For oral administration in adults.</u>
Recommended dose is 1 capsule to be administered once daily for 4 to 8 weeks.
P-PPi-L Capsules may be administered with or without food. The capsules should be swallowed whole with water and not to be opened, chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

P-PPi-L Capsules are contraindicated in the following:

- Patients with known hypersensitivity to pantoprazole or to any substituted benzimidazole derivative or to levosulpiride or to any component of the formulation.
- In patients receiving rilpivirine-containing products.
- Gastrointestinal bleeding and intestinal obstruction.
- Severe renal or hepatic insufficiency.
- Porphyrias.
- Alcohol intoxication.
- Certain tumors like phaeochromocytoma and pituitary prolactinoma.
- Concurrent use with levodopa or other antiparkinson drugs (including ropinirole).

4.4Special Warnings and Precautions for Use

Pantoprazole

Presence of Gastric Malignancy: In adults, symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a pantoprazole.

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

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that pantoprazole 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.

Risk of Bone Fractures: Proton pump inhibitors (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. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. 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.

Cutaneous and Systemic Lupus Erythematosus: Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. 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. The occurrence of CLE with previous PPI treatment may increase the risk of CLE with other PPIs. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. The majority of patients presented with rash. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and pantoprazole therapy should be stopped immediately. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks.

Cyanocobalamin (Vitamin B_{12}) Deficiency: Generally, daily treatment with any acid-suppressing medication over a long period of time (e.g., longer than 3 years) may lead to malabsorption of 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.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 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 PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), monitoring of magnesium levels prior to initiation of PPI treatment and periodically thereafter should be considered.

Levosulpiride

History of Breast Cancer: Levosulpiride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during levosulpiride therapy.

Prolongation of the QT Interval: Levosulpiride induces a prolongation of the QT interval. This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes. Levosulpiride should be used with caution in patients with cardiovascular disease or with a family history of QT prolongation.

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

Drugs Acting on CNS: Caution is advised when levosulpiride is administered concomitantly with other centrally acting drugs.

Alcohol: Concomitant intake of alcohol should be avoided during levosulpiride therapy as there is an increased chance of sedation.

Smoking: Smoking increases metabolism of the drug and thus, require higher dose of levosulpiride.

Parkinson's Disease: In patient with Parkinson's disease, levosulpiride use should be avoided and an alternative drug therapy should be considered.

Convulsions: Cases of convulsions, sometimes in patients with no previous history, have been reported. In patients requiring levosulpiride who are receiving anticonvulsant therapy, the dose of the anticonvulsant should not be changed.

Anticholinergic Effects: Levosulpiride has an anticholinergic effect and, therefore, should be used with caution in patients with a history of glaucoma, ileus, congenital digestive stenosis, urine retention or hyperplasia of the prostate.

Hypertensive Patients: Levosulpiride should be used with caution in hypertensive patients, especially in the elderly population, due to the risk of hypertensive crisis. Patients should be adequately monitored.

4.5Drug Interactions

Pantoprazole

Antiretroviral Drugs: 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. Concomitant use of rilpivirine-containing products with pantoprazole is contraindicated. Also, concomitant use of nelfinavir with pantoprazole should be avoided.
- Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity.
- There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.

Coumarin Anticoagulants/Warfarin: There have been post-marketing reports of increased international normalized ratio (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 and adjust the dose of warfarin, if needed, to maintain the target INR range.

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.

Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of pantoprazole therapy may be considered in some patients receiving high-dose of methotrexate.

Drugs for Which Gastric pH Can Affect Bioavailability (iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, and ketoconazole): Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may reduce absorption of other drugs where gastric pH is an important determinant of their bioavailability.

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 therapy and MMF. Use pantoprazole with caution in transplant patients receiving MMF.

Drug/Laboratory Tests Interactions

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.

Increased Chromogranin A (CgA) Lvel: Increase in CgA may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole 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, measurements should be repeated 14 days after cessation of pantoprazole treatment.

Levosulpiride

Antacids and Sucralfate: Bioavailability of levosulpiride is reduced if it is taken concomitantly with sucralfate and aluminum/magnesium-containing antacids. So, these medicines should not be taken along with levosulpiride. There should be a minimum 2 hour time lag between the two medicines.

Anticholinergic Drugs, Narcotics and Analgesic Drugs: The effect of levosulpiride on gastrointestinal motility can be antagonized by these drugs.

Antihypertensive Drugs: Concomitant use of levosulpiride may enhance the hypotensive effects of these drugs.

Anticholinergic Drugs: Concomitant administration may cause increase in incidence of anticholinergic side effects.

Levodopa/Antiparkinson Drugs (including ropinirole): There is reciprocal antagonism of effects between levodopa or antiparkinson drugs (including ropinirole) and levosulpiride. Levodopa reduces effects of levosulpiride; conversely, levosulpiride may decrease the efficacy of levodopa in the management of Parkinson's disease. Thus, concomitant use of these drugs is contraindicated.

Atomoxetine, Antiarrhythmics, Terfenadine, Chloroquine, Quinine, Cisapride, and Drugs Causing Hypokalemia (corticosteroids, laxatives, and diuretics like furosemide): Concurrent use of levosulpiride with these drugs may cause arrhythmia, especially prolonged QT interval.

Alcohol: Levosulpiride can potentiate the cognitive and motor effects of alcohol. Thus, concurrent use should be avoided.

Lithium: Increased risk of extrapyramidal effects. Discontinuation of both drugs is recommended at first signs of neurotoxicity.

4.6Use in Special Populations

Pregnant Women

Reproduction studies have been performed in rats at oral doses up to 88- times the recommended human dose and in rabbits at oral doses up to 16-times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. Use of sulpiride is not recommended during pregnancy because of the limited experience. No clinical data on exposed pregnancies are available for pantoprazole with levosulpiride combination therapy. Therefore, P-PPi-L Capsules are not recommended for use in pregnant women.

Lactating Women

Animal studies have shown that pantoprazole and its metabolites are excreted in the milk. Excretion of pantoprazole in human milk has also been reported (insufficient information). However, 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. Similarly, with pantoprazole, a risk to the newborns/infants cannot be excluded. Levosulpiride is known to be secreted in breast milk, so, its use should be restricted in breast-feeding women. P-PPi-L Capsules should not be used during breast feeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue/abstain from drug therapy, taking into account the benefit of the drug to the mother.

Paediatric Patients

Safety and efficacy of pantoprazole with levosulpiride combination therapy has not been established in paediatric patients. Thus, P-PPi-L Capsules are not recommended for use in children and adolescents below 18 years of age.

Geriatric Patients

No dosage adjustment is generally necessary in the elderly patients with normal renal function, but dose should be reduced if there is evidence of renal impairment. Elderly patients are more susceptible to postural hypotension, sedation, and extrapyramidal side effects. Thus, caution should be exercised in the elderly patients while on P-PPi-L therapy.

Renal Impairment Patients

Dosage modification is not necessary when pantoprazole is administered to patients with impaired renal function. However, levosulpiride dose need to be reduced and titrated in case of renal insufficiency. Thus, in patients with mild to moderate renal impairment, P-PPi-L Capsules should be used with caution and dose/dosage frequency may need to be reduced depending on the severity of the renal dysfunction. P-PPi-L Capsules are contraindicated in patients with severe renal impairment.

Hepatic Impairment Patients

In patients with severe liver impairment, a daily dose of pantoprazole 20 mg should not be exceeded. There is no information available on use of levosulpiride in patients with hepatic dysfunction. Thus, as a precautionary measure, P-PPi-L Capsules should be avoided in patients with hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Pantoprazole has no or negligible influence on the ability to drive and use machines. Adverse reactions such as dizziness and visual disturbances may occasionally occur with PPIs. Further, high doses of levosulpiride may cause drowsiness, numbness, or dyskinesia in some patients. Therefore, patients should avoid driving or operating machinery or not to engage in activities which require full mental alertness.

4.8Undesirable Effects

Pantoprazole

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in clinical practice.

Common adverse reactions reported with pantoprazole therapy in clinical trials with frequency > 2% include: Headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.

Additional adverse reactions reported in clinical trials with a frequency of ≤ 2% include:

Body as a Whole: Allergic reaction, pyrexia, photosensitivity reaction, facial edema.

Gastrointestinal: Constipation, dry mouth, hepatitis.

Hematologic: Leukopenia, thrombocytopenia.

Metabolic/Nutritional: Elevated creatine kinase (CK), generalized edema, elevated triglycerides, elevated liver enzymes.

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 proton pump inhibitors. The following adverse reactions have been identified during post-approval use of pantoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General Disorders and Administration Conditions: Asthenia, fatigue, malaise.

Hematologic: Pancytopenia, agranulocytosis.

Hepatobiliary Disorders: Hepatocellular damage leading to jaundice and hepatic failure.

Immune System Disorders: Anaphylaxis (including anaphylactic shock), SLE.

Infections and Infestations: *Clostridium difficile*-associated diarrhea.

Investigations: Weight changes.

Metabolism and Nutritional Disorders: Hyponatremia, hypomagnesemia.

Musculoskeletal Disorders: Rhabdomyolysis, bone fracture.

Nervous System: Ageusia, dysgeusia.

Psychiatric Disorders: Hallucination, confusion, insomnia, somnolence.

Renal and Urinary Disorders: Interstitial nephritis.

Skin and Subcutaneous Tissue Disorders: Severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema (Quincke's edema) and CLE.

Levosulpiride

The following side effects may occur with the use of levosulpiride:

- Acute muscular dystonia characterized by abnormal movements (twitching, tremor, etc.) of the hands, leg, tongue and facial muscles.
- Sedation or drowsiness (because of decrease in sensory inputs to reticular activating system).
- Increase in plasma prolactin levels manifested by breast enlargement (gynecomastia), production of milk (galactorrhea) and stopping of menstrual periods (amenorrhea).
- Neuroleptic malignant syndrome (characterized by hyperpyrexia, muscle rigidity, increased myoglobin and creatine kinase).
- Akathisia (uncontrollable desire to move about without any anxiety).
- Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of face, mouth and jaw. The reason for tardive dyskinesia is synthesis of newer dopamine receptors which are supersensitive to even a small amount of dopamine. This causes a decrease in cholinergic activity in the striatum followed by decrease in gamma-amino butyric acid (GABA) release. This decreased in inhibitory GABA is responsible for increased involuntary motor activity.
- Postural hypotension (because of autonomic blockade), tolerance develops to this effect after some time.
- Weight gain.
- Elevated liver transaminases.

4.9Overdose

Pantoprazole

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

Levosulpiride

Experience with levosulpiride overdose is limited. Extrapyramidal disturbances and sleep disorders may occur with higher doses and in patients who are sensitive to dopamine antagonists. Agitation, confusion and coma have also been reported with overdose of racemic drug i.e., sulpiride. Cardiovascular effect such as hypotension although rare, but may occur with levosulpiride overdose.

There is no specific antidote to levosulpiride. Sulpiride is partly removed by hemodialysis. Emetic drugs are unlikely to be effective in levosulpiride overdose. Treatment is only symptomatic. Appropriate supportive measures should therefore be instituted, close supervision of vital functions and cardiac monitoring (risk of QT interval prolongation and subsequent ventricular arrhythmias) is recommended until the patient recovers. If severe extrapyramidal symptoms occur anticholinergic drugs should be administrated. Overdose may be treated with alkaline osmotic diuresis and, if necessary, anti-parkinson drugs. Coma needs appropriate nursing, and cardiac monitoring is recommended until the patient recovers.

5. Pharmacological Properties

5.1 Mechanism of Action

Pantoprazole

Pantoprazole is a proton pump inhibitor (PPI) class of antisecretory agent. Pantoprazole is a lipophilic weak base that crosses the parietal cell membrane and enters the acidic parietal cell canaliculus where it becomes protonated, producing the active metabolite sulfenamide. Sulfenamide forms an irreversible covalent bond with two sites of the H+/K+-ATPase enzyme located on the gastric parietal cell. Thus, pantoprazole suppress the final step in gastric acid (hydrochloric acid – HCl) production by covalently binding to the H+/K+-ATPase enzyme (also called as proton pump) 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 duration of antisecretory effect that persists longer than 24 hours.

Levosulpiride

Prokinetic Effect: Levosulpiride is principally a dopamine D_2 antagonist. Dopamine has a direct relaxant effect on the gut by activating muscular D_2 receptors. Levosulpiride stimulates gut motility by blocking D_2 receptors in lower esophageal sphincter (LES) and stomach. Levosulpiride also acts as an agonist on serotonin 5-HT_4 receptors and thus, increases acetylcholine level which leads to increase in GI motility.

Antiemetic Effect: Levosulpiride exerts a selective antagonist activity on the D_2 receptors on neurons in the CNS (postrema area of 4^{th} ventricle) and thus, produces antiemetic effect. Levosulpiride is also a weak inhibitor of 5-HT_3 receptors. Levosulpiride also acts as a moderate agonist at the serotonergic (5-HT_4) receptor. This enhances its therapeutic efficacy in gastrointestinal disorders (reduction of nausea and vomiting).

5.2Pharmacodynamic Properties

Pantoprazole

With a single oral dose of 20 to 80 mg of pantoprazole, a dose-dependent decrease in gastric acid secretion occurs. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

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 receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, and gastrin).

The fasting gastrin values increase under pantoprazole. 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.

Levosulpiride

Levosulpiride, levo-enantiomer (biologically active form) of sulpiride, is a benzamide derivative. The levo-enantiomer shows better/similar pharmacological actions and lower incidence of toxic effects than both dextro as well as the racemic forms of the drug.
Due to its peripheral anti-dopaminergic action, levosulpiride exhibits gastrokinetic/prokinetic, antiemetic, and anti-dyspeptic effects. Levosulpiride act as a modulator of the motor activity of the upper digestive tract. Levosulpiride accelerates gastric emptying and improves gastrointestinal (GI) symptoms such as heart burn, regurgitation, etc. by selectively inhibiting dopaminergic receptors (D_2) in the submucosal and myoenteric plexus of the gastrointestinal tract (GIT) and chemoreceptor trigger zone (CTZ) of the central nervous system (CNS).

5.3Pharmacokinetic Properties

Pantoprazole

Absorption: P-PPi-L Capsules contains pantoprazole sodium as a gastro-resistant tablet. This is necessary because, like other PPIs, pantoprazole is acid-labile. Absorption of pantoprazole, therefore, begins only after the tablet leaves the stomach.
After administration of a single or multiple oral doses of pantoprazole 40 mg, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C_{max} was 2.5 mcg/ml. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increases in a dose-dependent manner (with dose range from 10 to 80 mg). Pantoprazole does not accumulate, and its pharmacokinetics is unaltered with multiple daily dosing. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%.
Effect of Antacid/Food: Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.
Distribution: The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 liters, distributing mainly in extracellular fluid. The plasma protein binding of pantoprazole is about 98%, primarily to albumin.
Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. 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.
Excretion: Renal elimination represents the major route of excretion (about 80 %) for the metabolites of pantoprazole, the rest is excreted with the faeces. There is no renal excretion of unchanged pantoprazole. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with sulphate. Following oral administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

Levosulpiride

Pharmacokinetics of levosulpiride in sustained release formulation is not available. Conventional formulation of levosulpiride (i.e., immediate release) has following pharmacokinetic properties:

Levosulpiride when administered orally exhibited linear pharmacokinetic properties over the dose range of 25 to 100 mg. The bioavailability of levosulpiride when given orally is about 30%.

Sulpiride is slowly absorbed from the gastrointestinal tract with peak plasma concentrations are attained 3 to 6 hours after oral dose. After repeated administration, steady state was reached on day 4 of multiple dosing. Sulpiride is about 40% bound to plasma proteins and is reported to have a plasma half-life of about 8 to 9 hours. Levosulpiride is mainly excreted through the renal route.

6. Nonclinical Properties

6.1 Animal Toxicology

Pantoprazole

Carcinogenesis: 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 with 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, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day of pantoprazole, 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.

Mutagenesis: 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.

Impairment of Fertility: 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).
Teratogenicity: Reproduction studies have been performed in rats at oral pantoprazole doses up to 450 mg/kg/day (about 88 times the recommended human dose based on body surface area) and in rabbits at oral doses up to 40 mg/kg/day (about 16 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals. The studies have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

Levosulpiride

The values expressed as LD50 acute toxicity after oral administration in mice, rats and rabbits were 2450 mg / kg, 2600 mg / kg and greater than 1500 mg / kg.
Subacute toxicity tests were conducted by administering the active ingredient in rat, rabbit and dog, daily, for 12-13 weeks. The appearance of any toxic symptoms was not observed at doses of: 25 mg / kg s.c. and 300 mg / kg p.o. in the rat; 250 mg / kg p.o. and 12.5 mg / kg i.m. in rabbits; and 50 and 100 mg / kg p.o. in the dog.
To evidentiate the chronic toxicity after administration of the drug for 180-190 days, the following doses were well tolerated: 100 mg / kg p.o. and 20 mg / kg s.c. in the rat; 10 mg / kg i.m. in rabbits; and 20 mg / kg p.o. in the dog.
Studies performed in rats and mice, administering the medicine at a dose higher than that expected for man, have shown that levosulpiride do not possess carcinogenic properties.
Studies carried out in rats and rabbits have shown that the medicine is not teratogenic.
In vitro tests have ruled out that levosulpiride possesses mutagenic properties.

7. Description

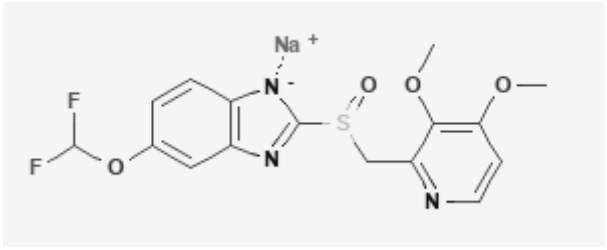
P-PPi-L Capsules are Blue/Blue hard gelatin capsules of size “0”, containing one dark yellow coloured, round, biconvex, plain on both sides & enteric coated (Pantoprazole tablet) & one white, round, biconvex, plain on both sides and uncoated sustained release tablet (Levosulpiride tablet SR).

Each capsule of P-PPi-L contains 40 mg of pantoprazole (in gastro-resistant form) and 75 mg of levosulpiride (in sustained release form) for oral administration in adults.

Pantoprazole Sodium

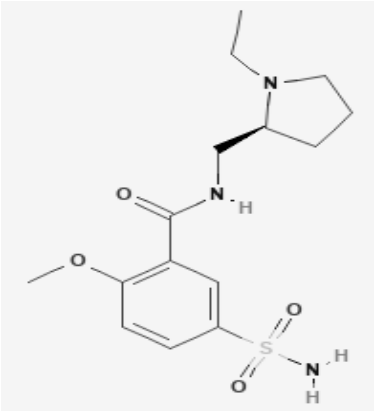
Pantoprazole sodium is the sodium salt form of pantoprazole. Pantoprazole is a substituted benzimidazole, proton pump inhibitor (PPI) class of antisecretory agents which suppresses gastric acid production.
Pantoprazole sodium is a white to off-white crystalline powder. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.
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:



Levosulpiride

Levosulpiride is the active levorotatory enantiomer of the racemic drug sulpiride, a substituted benzamide. Levosulpiride is a dopaminergic antagonist with prokinetic, antiemetic, antidepressant, and antipsychotic properties.
Levosulpiride is a white to cream colour powder practically insoluble in water, sparingly soluble in methanol, and slightly soluble in alcohol and in methylene chloride.
Molecular Weight: 341.4 g/mol.
Molecular Formula: C15H23N3O4S.
Chemical Name: N-[[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-sulfamoylbenzamide.
Structural Formula:



Inactive ingredients (excipients) of P-PPi-L Capsules contain Maize Starch, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Sodium Carbonate, Hydroxy Propyl Methyl Cellulose, Polysorbate 80, Magnesium Stearate, Talcum, Crospovidone, Akoat-512, Procoat ECM Aqua, Colour Tartrazine, Methocel K4M, Polyvinyl Pyrrolidone K-30, Isopropyl Alcohol & Hard Gelatin Capsule.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life
24 Months

8.3Packaging Information
15 capsules per alu-alu blister.

8.4Storage and Handling Instructions
Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information
Administration Instructions

- Instruct patients to take P-PPi-L Capsules exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting to your doctor.
- Instruct patients to swallow P-PPi-L Capsules as a whole with water and not to open, chew or crush the capsules.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take 2 doses/capsules at the same time to make up for the missed dose.
- Pregnant women should not use this medicine.
- Advise nursing mothers to avoid use of this medicine during lactation or not to breastfeed their infants while on drug therapy.
- This medicine is not recommended for use in children.
- Instruct patients not to share this medication with other people even though symptoms are similar. It may harm them.
- Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. P-PPi-L Capsules and certain other medicines can interact with each other causing serious side effects.

10. Details of Manufacturer
Akums Drugs & Pharmaceuticals Ltd.
At: Plot No. 26A, 27-30, Sector - 8A, I.I.E., SIDCUL,
Ranipur, Haridwar - 249 403, Uttarakhand.

11. Details of Permission or License Number with Date
Mfg. Lic. No. : 4/UA/LL/2014, Date of Product Permission: 13/02/2019

12. Date of Revision
February 2023.

Marketed by:

EXCEL BLUE CROSS || EXCEL

Division of

BLUE CROSS LABORATORIES PVT LTD.

A-12, M.I.D.C., NASHIK-422 010.

Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.