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

Rabeprazole Sodium (GR) and Levosulpiride (SR) Capsules
(Brand Name: R-PPi®-L Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Rabeprazole Sodium IP ……..…..…… 20 mg
(as Gastro-resistant tablet)
Colours: Red Oxide of Iron & Titanium Dioxide IP.
Levosulpiride …… 75 mg
(as uncoated sustained release tablet)
Excipients ……..…… q.s.
Colours used in capsule shell : Sunset Yellow FCF, Quinoline Yellow WS,
Titanium Dioxide IP.
Methylparaben and Propylparaben used as Antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Rabeprazole 20 mg (in a gastro-resistant form) with levosulpiride 75 mg (in a sustained release form) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

R-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.
R-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

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

- Patients with known hypersensitivity to rabeprazole 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

Rabeprazole

Gastric Malignancy: In adults, symptomatic response to rabeprazole therapy does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with rabeprazole. 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 proton pump inhibitor (PPI).

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

Cyanocobalamin (Vitamin B_{12}) Deficiency: Daily treatment with acid-suppressing drugs over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin 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 in patients treated with rabeprazole.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement as well as 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 serum magnesium levels prior to initiation of PPI treatment and periodically thereafter should be considered.

Risk of Bone Fractures: 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 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 of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that PPI therapy like rabeprazole 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.

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 rabeprazole therapy should be stopped immediately. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Thrombocytopenia and Neutropenia: There have been post-marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole therapy.

Hepatic Effects: Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported in post-marketing studies. In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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

Rabeprazole

Antiretroviral Drugs: The effect of PPI on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

1) Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with rabeprazole may reduce antiviral effect and promote the development of drug resistance.
    - **Rilpivirine-Containing Products:** Concomitant use with rabeprazole is contraindicated.
    - **Atazanavir:** Co-administration of atazanavir 300 mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other PPIs. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.
    - **Nelfinavir:** Avoid concomitant use with rabeprazole.
2) Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with rabeprazole may increase toxicity. It is recommended to monitor for potential saquinavir toxicities.
3) There are other antiretroviral drugs which do not result in clinically relevant interactions with rabeprazole.

Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole): Rabeprazole produces a profound and long lasting inhibition of gastric acid secretion. An interaction with drugs whose absorption is pH dependent may occur. Rabeprazole can reduce the absorption/bioavailability of such drugs due to its effect on reduction of intragastric acidity.

- **Ketoconazole/Itraconazole:** Co-administration of rabeprazole with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. In healthy adult subjects, co-administration of rabeprazole 20 mg at steady state with a single 400 mg of ketoconazole resulted in approximately an average of 31% reduction in both C_{max} and AUC of ketoconazole. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.
- **Mycophenolate Mofetil:** Co-administration of PPIs with mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant

patients receiving PPIs and mycophenolate mofetil. Use rabeprazole with caution in transplant patients receiving mycophenolate mofetil.

Antacids: In clinical trials, antacids were used concomitantly with the administration of rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.

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

Warfarin: Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased international normalized ratio (INR) and prothrombin time in patients receiving a PPI and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Thus, patients treated with rabeprazole and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Digoxin: When rabeprazole and digoxin are administered concomitantly, there is potential for increased exposure of digoxin. Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore, its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged or while using rabeprazole, consider an alternative antiplatelet therapy.

Tacrolimus: Potentially increased exposure of tacrolimus has been reported, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19; thus, monitoring of plasma levels of tacrolimus is advised. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentration.

Drug/Laboratory Tests Interactions

Increased Chromogranin A (CgA) Levels: Increased CgA level may interfere with investigations for neuroendocrine tumors. To avoid this interference, rabeprazole 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 PPI treatment.

Secretin Stimulation Test: Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma. Temporarily stop treatment with rabeprazole at least 14 days before assessing to allow gastrin levels to return to baseline.

False Positive Urine Tests for Tetrahydrocannabinol (THC): There have been reports of false positive urine screening tests for THC in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

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 performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole, although low feto-placental transfer occurs in rats. No evidence of adverse developmental effects were seen in animal reproduction studies with rabeprazole administered during organogenesis at 13 and 8-times the human area under the plasma concentration-time curve (AUC) at the recommended dose for GERD, in rats and rabbits, respectively. Use of sulpiride is not recommended during pregnancy because of the limited experience. No clinical data on exposed pregnancies are available for rabeprazole with levosulpiride combination therapy. Therefore, R-PPi-L Capsules are not recommended for use in pregnant women.

Lactating Women

It is not known whether rabeprazole is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole is however excreted in rat mammary secretions. Levosulpiride is known to be secreted in breast milk, so, its use should be restricted in breast-feeding women. R-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 rabeprazole with levosulpiride combination therapy has not been established in paediatric patients. Thus, R-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 population while on rabeprazole with levosulpiride combination therapy.

Renal Impairment Patients

With rabeprazole, no dosage adjustment is necessary in patients with renal impairment. However, levosulpiride dose need to be reduced and titrated in case of renal insufficiency.

Thus, in patients with mild to moderate renal impairment, R-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. R-PPi-L Capsules are contraindicated in patients with severe renal impairment.

Hepatic Impairment Patients

Administration of rabeprazole to patients with mild to moderate hepatic impairment resulted in increased exposure and decreased elimination; however, no dosage adjustment is necessary in these patients. There is no information available on use of levosulpiride in patients with hepatic dysfunction. Thus, as a precautionary measure, R-PPi-L Capsules should be avoided in patients with hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Rabeprazole 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 therapy which may impair patient's mental alertness. 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 that require full mental alertness.

4.8Undesirable Effects

Rabeprazole

Clinical Trials Experience

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

In controlled clinical trials, the most commonly reported adverse reactions (≥ 2%) in patients treated with rabeprazole versus placebo include the following: Pain (3% vs. 1%), pharyngitis (3% vs. 2%), flatulence (3% vs. 1%), infection (2% vs. 1%), and constipation (2% vs. 1%).

Less common adverse reactions seen in controlled clinical trials (< 2% of patients treated with rabeprazole and greater than placebo) and for which there is a possibility of a causal

relationship to rabeprazole, include the following: Headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, elevated hepatic enzymes, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

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 rabeprazole. 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:

Blood and Lymphatic System Disorders: Agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia.

Ear and Labyrinth Disorders: Vertigo.

Eye Disorders: Blurred vision.

Hepatobiliary Disorders: Jaundice.

Immune System Disorders: Anaphylaxis, angioedema, systemic lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis (sometime fatal).

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

Investigations: Increases in prothrombin time/INR (in patients treated with concomitant warfarin), elevations in thyroid stimulating hormone (TSH).

Metabolism and Nutrition Disorders: Hyperammonemia, hypomagnesemia.

Musculoskeletal System Disorders: Bone fracture, rhabdomyolysis.

Nervous System Disorders: Coma.

Psychiatric Disorders: Delirium, disorientation.

Renal and Urinary Disorders: Interstitial nephritis.

Respiratory, Thoracic and Mediastinal Disorders: Interstitial pneumonia.

Skin and Subcutaneous Tissue Disorders: Severe dermatologic reactions including bullous and other drug eruptions of the skin, cutaneous lupus erythematosus, erythema multiforme.

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

Rabeprazole

Experience with deliberate or accidental overdose with rabeprazole is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention.

No specific antidote is known. Rabeprazole is extensively protein bound and is, therefore, not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

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

Rabeprazole

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole, proton-pump inhibitors - PPIs). As a weak base, rabeprazole is rapidly absorbed following oral dose and is concentrated in the acidic environment of the parietal cells. In gastric parietal cells (at pH 1.2), rabeprazole is converted to the active ‘sulphenamide’ form through ‘protonation’ and it subsequently reacts with the available cysteines on the proton pump.

Rabeprazole suppress gastric acid (hydrochloric acid – HCl) secretion by inhibiting the gastric H+/K+-ATPase enzyme at the secretory surface of the gastric parietal cell. Because

this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

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

Rabeprazole

Oral administration of a 20 mg dose of rabeprazole provides rapid and effective reduction of gastric acid secretion. The onset of the antisecretory effect occurs within one hour, with the maximum effect occurring within 2 to 4 hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action of rabeprazole is much longer than its pharmacokinetic half-life (approximately one hour). This effect is probably due to the prolonged binding of rabeprazole to the parietal H+/K+-ATPase enzyme. The inhibitory effect of rabeprazole on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after 3 days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

With once daily doses of rabeprazole 10 or 20 mg, serum gastrin levels increases in 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

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

Rabeprazole

The pharmacokinetics (C_{max} and AUC) of rabeprazole are linear over the range of 10 mg to 40 mg. There is no significant accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing.

Absorption: R-PPi-L Capsules contains rabeprazole sodium as a gastro-resistant tablet. This is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore, begins only after the tablet leaves the stomach. After oral administration of rabeprazole 20 mg, peak plasma concentrations (C_{max}) occur over a range of 2 to 5 hours (T_{max}). Absolute bioavailability for rabeprazole 20 mg (compared to intravenous administration) is approximately 52% (because of extensive pre-systemic metabolism). Additionally, the bioavailability does not appear to increase with repeat dose administration of rabeprazole.

Effect of Food: With rabeprazole, there was no clinically relevant interaction with food. Neither food nor the time of day of administration affects the absorption of rabeprazole. Thus, rabeprazole may be administered without regard to timing of meals.

Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. Rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. A significant portion of rabeprazole is also metabolized via systemic non-enzymatic reduction to a thioether compound.

Excretion: Following a single 20 mg oral dose of rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid, glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. No unchanged rabeprazole was recovered in the urine or feces. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 ml/min.

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

Rabeprazole

Carcinogenesis: In an 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg•hr/ml which is 1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 μg•hr/ml) at the recommended dose for GERD (20 mg/day).

In a 28-week carcinogenicity study in p53+/- transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17 to 24 times the human exposure at the recommended dose for GERD.

In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60, and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μg•hr/ml which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μg•hr/ml (0.2 times the human exposure at the recommended dose for GERD).

Mutagenesis: Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test, and the mouse lymphoma cell forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Impairment of Fertility: Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/ml, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Developmental Toxicity: Embryo-fetal developmental studies have been performed in rats during organogenesis at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/ml, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/ml, about 8 times the human exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

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.

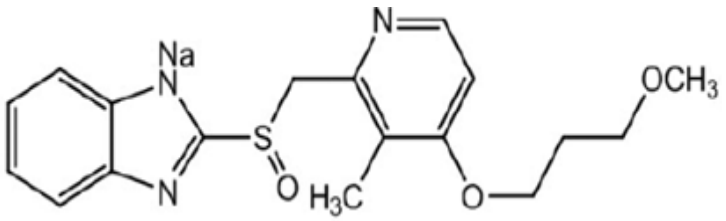
7. Description

R-PPi-L Capsules are Golden Yellow / Golden Yellow hard gelatin capsule of size 0 containing one light brown coloured, round, biconvex, both side plain & enteric coated tablet (Rabeprazole tablet), one white to off white round, biconvex, both side plain & uncoated sustained release tablet (Levosulpiride tablet) & white small dummy pellets.

Each capsule of R-PPi-L contains 20 mg of rabeprazole (in a gastro-resistant form) and 75 mg of levosulpiride (in a sustained release form) for oral administration in adults.

Rabeprazole Sodium

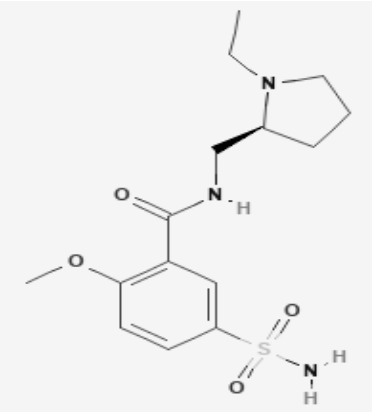
Rabeprazole sodium is a substituted benzimidazole, proton pump inhibitor (PPI) class of antisecretory agents. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform, and ethyl acetate and insoluble in ether and n-hexane.
Molecular Weight: 381.42 g/mol.
Molecular Formula: C18H20N3NaO3S
Chemical Name: 2-[[[4-(3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt..
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 R-PPi-L Capsules contain Light Magnesium Oxide, Mannitol, Crospovidone, Hydroxy Propyl Cellulose, Isopropyl Alcohol, Magnesium Stearate, Talcum, Croscarmellose Sodium, Instacoat Sol, Methylene Chloride, Colour Red Oxide of Iron, Instacoat EN- Super IV, Methocel K4M, Polyvinyl Pyrrolidone K -30, Colloidal Silicon Dioxide & 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 R-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 R-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.
- Instruct patients not to use this medicine if you are pregnant.
- 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. R-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.
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