For the use of a Registered Medical Practitioner only

1. GENERIC NAME AND BRAND NAME

Enteric coated Rabeprazole Sodium and Levosulpiride SR Capsules
Enliva®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:
Rabeprazole Sodium I.P (as enteric coated pellets) 20mg
Levosulpiride (as sustained release tablet) 75mg
Colours: Titanium Dioxide I.P., Ferric oxide (Red) USP-NF & Ferric oxide (Black) USP-NF
Colours in empty Capsule shell: Brilliant Blue FCF, Erythrosine, Carmoisine & Titanium Dioxide I.P.

DOSAGE FORM AND STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

For the treatment of Gastro-esophageal Reflux Disease (GERD).

4.2 POSOLOGY AND MEHTOD OF ADMINISTRATION

One capsule of Rabeprazole and Levosulpiride ER should be taken once daily at least one hour before meal. The duration of administration should be based on available safety and efficacy data specific to the defined indication.

4.3 CONTRAINDICATIONS

• Known hypersensitivity to rabeprazole, substituted benzimidazoles, levosulpiride or any of the excipients
• Pheochromocytoma, as it can cause hypertensive attack probably due to release of catecholamine from tumor; such attacks can be controlled with phentolamine
• Epilepsy
• In manic conditions and in the manic stages of manic-depressive psychoses.
- Concomitant prolactin dependent tumors like pituitary gland prolactinomas
  •Breast cancer
  • Pregnancy and lactation
  • Association with levodopa

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rabeprazole

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with rabeprazole is instituted, as treatment with rabeprazole may alleviate symptoms

and delay diagnosis Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance

Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and possibly Clostridium difficile.

As demonstrated with other PPIs, prolonged use may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of Vitamin B12 deficiency.

Levosulpiride

Extrapyramidal reactions, mainly akathisia, and for that dosage reduction warranted. Increased motor agitation at higher dosages Narcoleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in association with other antipsychotic drugs. NMS is associated with hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. In such an event, or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs must be discontinued.

The treatment of NMS involves immediate discontinuation of administration of antipsychotic drugs and establishment of intensive symptomatic therapy (particular care should be taken to reduce hyperthermia and correct the dehydration). If resumption of treatment with antipsychotic drugs becomes essential, the patient should be carefully monitored. Levosulpiride should be used with caution in patients with manic states such as in the manic phase of manic depressive psychosis. Caution is advised when the drug is administered to patients with cerebrovascular events including risk factors for stroke. Caution is also advised when levosulpiride is given to patients with cardiac insufficiency.

Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects. The dose should be reduced if there is evidence of renal impairment. Caution is advised when there is prolongation of QTc interval or factors that may predispose QTc interval prolongation (Bradycardia, hypokalemia, congenital QTc prolongation, decreased intracardiac conduction). Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

4.5 DRUG INTERACTIONS

Rabeprazole

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. 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. 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. Co-administration of atazanavir 300mg/ritonavir 10mg with omeprazole (40 mg once daily) or atazanavir 400mg with lansoprazole (60mg 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 proton pump inhibitors Therefore PPIs including rabeprazole, should not be co-administered with atazanavir.

Levosulpiride

Caution is advised when levosulpiride is taken concomitant1y with other centrally acting drugs. It can potentiate the cognitive and motor effects of alcohol. CNS depressants including narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives, lithium increases the risk of extrapyramidal side effects. Caution is advised with medications that may predispose QTc interval prolongation that include • Bradycardia inducing medications: Beta blockers, calcium channel blockers (verapamil, diltiazem), clonidine, and digitalis • Medications which induce electrolyte imbalance (particularly hypokalemia), hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoiss and tetracosectides. • Class Ia antiarrhythmic agents such as quinidine and disopyramide • Class III antiarrhythmic agents such as amiodarone and sotalol • Other medications such as pimozide, haloperidol; methadone, imipramine antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine and pentamidine Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension. The effect of levosulpiride on gastrointestinal motility can be antagonized by anti-cholinergic drugs; narcotics and analgesic drugs. Antacids or sucralfate: The absorption of sulpiride is decreased alter co-administration; hence, sulpiride should be administered two hours before these drugs. Sulpiride may reduce the effectiveness of ropinorole.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnant Women: Pregnancy Category B: The safety of rabeprazole treatment in pregnancy has not been established. Rabeprazole should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus. Levosulpiride should not be used during presumed or confirmed pregnancy.

Nursing Women: It is not known whether rabeprazole is excreted in human milk. Rabeprazole tablets should not be given to nursing mothers unless the expected benefits outweigh the potential risks to the infant. Levosulpiride should not be used during the lactation period.

Pediatrics (<18 years of age): The safety and efficacy of rabeprazole have not been established in children under the age of 18 years.

Geriatrics: Adverse events and laboratory test abnormalities in elderly patients using rabeprazole occurred at rates similar to those in younger patients. No dose adjustment is required in elderly patients.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE REACTIONS

Rabeprazole:

The following adverse events have been reported from clinical trials and post-marketed experience Frequencies are defined as: common (>1/100, <1/10), uncommon (> 1/1,000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000),

System Organ Class

Infections and infestations

Common: Infection

Blood and the lymphatic system disorders

Rare: Neutropenia, leucopenia, Thrombocytopenia, Leucocytosis

Immune system disorders

Rare: Hypersensitivity (Includes facial swelling, hypotension and dyspnoea)

Metabolism and nutrition disorders

Rare: Anorexia

Not Known: Hyponatremia

Psychiatric disorders

Common: Insomnia Uncommon: Nervousness

Rare: Depression

Not Known: Confusion

Nervous system disorders

Common: Headache, Dizziness

Uncommon: Somnolence Eye disorders

Rare: Visual disturbance

Vascular disorders

Respiratory, thoracic and mediastinal disorders

Common: Cough, Pharyngitis, Rhinitis

Uncommon: Bronchitis, Sinusitis

Gastrointestinal disorders
Common: Diarrhoea Vomiting, Nausea Abdominal pain, Constipation, Flatulence Uncommon: Dyspepsia, Dry mouth, Eructation Rare: Gastritis, Stomatitis, Taste disturbance
Hepato-biliary disorders
Rare: Hepatitis, Jaundice, Hepatic encephalopathy
Skin and subcutaneous tissue disorders
Uncommon: Rash, Erythema
Rare: Pruritus, Sweating, Bullous reactions
Very Rare: Erythema multi form, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)
Musculoskeletal, connective tissue and bone disorders
Common: Non-specific pain, Back pain Uncommon: Myalgia, Leg cramps, Arthralgia Renal and urinary disorders
Uncommon: Urinary tract infection
Rare: Interstitial nephritis, Acute kidney injury

Reproductive system and breast disorders
Not Known: Gynaecomastia
General disorders and administration site conditions
Common: Asthenia, Influenza like illness
Uncommon: Chest pain, Chills, Pyrexia
Investigations
Uncommon: Increased hepatic enzymes (Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis)
Rare: Weight increased

Levosulpiride
Cardiovascular disorders - Postural hypotension - QT Interval prolongation and ventricular arrhythmias such as torsade de pointes and ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death.
Endocrine disorders - Hyperprolactinaemia, reversible effects of levosulpiride on functioning of hypothalamic pituitary gonadal axis
General disorders and administration site conditions –
Neuroleptic malignant syndrome - Weight gain
Hepatobiliary disorders - Increase in hepatic enzymes
Nervous system disorders - Sedation or drowsiness Insomnia has been reported - Extrapyramidal symptoms and related disorders - Parkinsonism and related symptoms: tremor, hypertonia, hypokinesia, hypersalivation - Acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus). Akathisia. These symptoms are generally reversible upon administration of antiparkinsonian medication - Tardive dyskinesia (characterized by rhythmic, involuntary movements primarily of the tongue and/or tile face) have been reported, as with all neuroleptics, alter a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation or the symptoms - Convulsions have been reported, in particular in patients with epilepsy

Reproductive system and breast disorders - Disorders related to hyperprolactinaemia - Galactorrhoea - Amenorrhoea - Gynaecomastia - Breast enlargement and breast pain - Orgasmic dysfunction, erectile dysfunction, change in libido Skin and subcutaneous tissue disorders - Maculo-papular rash Vascular disorders - Venous thromboembolism, pulmonary embolism and deep vein thrombosis been reported with antipsychotic: drugs-frequency unknown

4.9 OVERDOSE

Rabeprazole

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60mg twice daily, or 160mg 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 sodium is extensively protein bound and is therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized

Levosulpiride

The clinical manifestation of poisoning depends on amount of dose ingested. Symptoms like, restlessness, clouding of consciousness extrapyramidal symptoms, agitation, confusion, hypotension, rarely coma at higher dose are reported. It is partly removed by hemodialysis. There is no specific antidote to poisoning of levosulpiride, only supportive measures should be undertaken and close monitoring of cardiac functions and vitals is recommended. Overdosage should be treated with alkaline diuresis, antiparkinsonian drugs, if necessary, anticholinergic in case of severe extrapyramidal symptoms

5.0 PHARMACOLOGIC PROPERTIES

5.1 MECHANISM OF ACTION

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonist properties but suppress gastric acid secretion by the specific inhibition of the H^+/K^+-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Levosulpiride is a prokinetic agent with dual mechanism of action. It blocks the enteric dopamine (D2) receptors (both neuronal & muscular) and also acts as an agonist at serotonin (5-HT4) receptor. Both the above actions increase the release of acetylcholine (Ach). Ach increases GI peristalsis and also increases lower esophageal sphincter pressure thereby preventing reflux of GI contents towards esophagus. It also inhibits transient lower esophageal sphincter pressure thereby preventing reflux of GI contents towards esophagus. It also inhibits transient lower esophageal sphincter relaxations (TLESRs).

Pharmacodynamics

Rabeprazole is a substituted benzimidazole proton-pump inhibitor that suppresses gastric acid secretion by inhibiting the gastric H+, K+ATPase at the secretory surface of the gastric parietal cell. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. The effect

dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Levosulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. Levosulpiride is a prokinetic drug which amplifies the lower esophageal sphincter pressure . The prokinetic effect of Levosulpiride is mediated through the blockade of enteric (neuronal and muscular) inhibitory dopamine D2 receptors. Levosulpiride also acts as a reasonable agonist at the 5-HT4 receptor

5.2 PHARMACOKINETIC PROPERTIES

Rabeprazole Absorption: Being enteric coated, Rabeprazole Sodium absorption begins only after it leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours (1.6 - 5.0 hours) after a 20mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10mg to 40mg. Absolute bioavailability of an oral 20mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration**.**

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. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affects the absorption of rabeprazole sodium.

Distribution: Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion: Rabeprazole sodium, is metabolized through the cytochrome P450 (CYP450) hepatic drug metabolising system. Rabeprazole sodium is metabolized by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In *in vitro* studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in vitro studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone.
(M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma. Following a single 20mg 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

Gender: After adjustment for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20mg dose of rabeprazole.

Renal dysfunction: In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance 5ml/min/1.73m2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the Cmax in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice than in healthy volunteers.

Hepatic dysfunction: Following a single 20mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20mg dose daily for 7 days the AUC had increased to only 1.5-fold and the Cmax to only 1.2-foId. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Elderly: Elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20mg of rabeprazole sodium, the AUC approximately doubled, the Cmax increased by 60% and t½ increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.

CYP2C19 Polymorphism: Following a 20mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½, which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst Cmax had increased by only 40%.

Levosulpiride

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%. The time to peak concentration is 3 to 9 hours with median tmax 5.5 hours. The oral AUC value for levosulpiride extended release tablet for a dose of 200 mg is 6050 ng.hr/ml. Levosulpiride displays a protein binding of about 14% and a volume of distribution of 1 to 2.7 L/kg which is similar in elderly and younger subjects.

Metabolism 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. The lack of hepatic metabolism makes metabolic interactions with cytochrome P-450 related substrates very unlikely.

The elimination half life ranges from 4.7 to 14.6 hours for oral 200mg dose of levosulpiride ER tablet. The elimination half life is prolonged in patients with renal impairment. The peak concentrations, time to peak levels and the elimination half life is similar in younger and elderly patients.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Non-clinical effects were observed with Rabeprazole only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.
Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but *in vivo* micronucleus and *in vivo* and *in vitro* DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans
The values expressed as LD50 acute toxicity after oral administration of Levosulpiride in mice, rats and rabbits were 2450 mg / kg, 2600 mg / kg and greater than 1500 mg / kg. LD 50 values:
in the mouse : 210 mg / kg, via i.p,
in the rat via i.p. and i.v. :to 270 mg / kg and 53 mg / kg, respectively,
in the rabbit via i.v.: to 42 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 sc and 300 mg / kg p.o. in the rat,
250 mg / kg p.o. and 12.5 mg / kg i.m. in rabbits,
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 the medicine possesses mutagenic properties.

7. DESCRIPTION
ENLIVA is supplied for oral administration, as a hard gelatin capsules. Each hard gelatin capsule of ENLIVA contains Rabeprazole Sodium (as enteric coated pellets) 20mg & Levosulpiride (as sustained release tablet) 75mg.

8. PHARMACEUTICAL PARTICULARS
8.1 INCOMPATIBILITIES
Not applicable

8.2 SHELF-LIFE
Refer Pack

8.3 PACKAGING INFORMATION
Refer Pack

8.4 STORAGE CONDITION AND HANDING INSTRUCTIONS
Refer Pack

9. PATIENT COUNSELLING INFORMATION

How to Take Rabeprazole Sodium and Levosulpiride Capsules

Always take this medicine exactly as your doctor has told you. Patients should be cautioned that capsule should be swallowed whole. Your doctor will decide how long you will need to take this medicine. Symptoms usually resolve with 3-4 days of taking this medicine. The capsule should not be chewed, crushed, or split. Rabeprazole Sodium and Levosulpiride Capsules can be taken with or without food. Levosulpiride may cause drowsiness in some patients, especially at higher doses, thus patients should be advised to exercise caution when driving or operating machinery. Advise patient to immediately report and seek care for diarrhea that does not improve. This may be a sign of Clostridium difficile associated diarrhea.

10. DETAILS OF MANUFACTURER:

Refer Pack for manufacturer details.

MARKETED BY:

Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER

Refer Pack for Permission/License details

12. DATE OF REVISION

Version 4.0, dated 11th June 2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com