SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rabeprazole Sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Enteric Coated tablet contains:
Rabeprazole Sodium……10 mg
Excipients…….q.s.
Colour: Titanium Dioxide BP and Iron Oxide Yellow

Each Enteric Coated tablet contains:
Rabeprazole Sodium……20 mg
Excipients…….q.s.
Colour: Titanium Dioxide BP and Iron Oxide Yellow

3. PHARMACEUTICAL FORM

Enteric coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rabeprazole tablets are indicated for the treatment of:

- Active duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD).
- Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance)
- Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
- Zollinger-Ellison Syndrome

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with peptic ulcer disease.

4.2 Posology and method of administration

Adults/elderly:

Active Duodenal Ulcer and Active Benign Gastric Ulcer: The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20mg to be taken once daily in the morning.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing. Most patients with active benign gastric ulcer heal within six weeks. However again a few patients may require an additional six weeks of therapy to achieve healing.

Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is 20mg to be taken once daily for four to eight weeks.
Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance): For long-term management, a maintenance dose of Rabeprazole 20 mg or 10mg once daily can be used depending upon patient response.

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD): 10mg once daily in patients without oesophagitis. If symptom control has not been achieved during four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 10mg once daily when needed.

Zollinger-Ellison Syndrome: The recommended adult starting dose is 60 mg once a day. The dose may be titrated upwards to 120mg/day based on individual patient needs. Single daily doses up to 100mg/day may be given. 120mg dose may require divided doses, 60mg twice daily. Treatment should continue for as long as clinically indicated.

Eradication of H. pylori: Patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended.

Rabeprazole 20 mg twice daily + clarithromycin 500mg twice daily and amoxicillin 1g twice daily.

Renal and hepatic impairment: No dosage adjustment is necessary for patients with renal or hepatic impairment.

See section 4.4 Special Warnings and Precautions for Use of Rabeprazole in the treatment of patients with severe hepatic impairment.
Children: Rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

Method of administration:
For indications requiring once daily treatment Rabeprazole tablets should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

Patients should be cautioned that the Rabeprazole tablets should not be chewed or crushed, but should be swallowed whole.

4.3 Contraindications

Rabeprazole is contra-indicated in patients with known hypersensitivity to rabeprazole sodium, or to any excipient used in the formulation. Rabeprazole is contra-indicated in pregnancy and during breast feeding.

4.4 Special warnings and precautions for use

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole Tablets.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.

Patients should be cautioned that Rabeprazole tablets should not be chewed or crushed, but should be swallowed whole.

Rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

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.

Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorization. In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of Rabeprazole in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole is first initiated in such patients.

Co-administration of atazanavir with Rabeprazole is not recommended (see section 4.5).

Treatment with proton pump inhibitors, including Rabeprazole, may possibly increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile* (see section 5.1).

Proton pump inhibitors, 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 recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. 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.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like rabeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Concomitant use of Rabeprazole with Methotrexate

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

Influence on vitamin B12 absorption

Rabeprazole sodium, as all acid blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or a- chlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long term therapy or if respective clinical symptoms are observed.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors 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 the health care professional should consider stopping Rabeprazole Sodium. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, rabeprazole sodium treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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 (see Section 4.4).

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

4.6 Pregnancy and lactation

Pregnancy:

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole is contraindicated during pregnancy.

Lactation:

It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore Rabeprazole should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 Undesirable effects

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial 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), Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations	Infection				
Blood and the lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity[1,2]		
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipati	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		

	on Flatulence fundic glandpolyps(benign)				
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		

Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacutecutaneous lupus erythematosus (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia fracture of the hip, wrist or spine (*see section 4.4*)			
Renal and urinary disorders		Urinary tract infection	Interstitial nephritis		
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

[1] Includes facial swelling, hypotension and dyspnoea

[2] Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

[3] Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole 10 mg is first initiated in such patients (see section 4.4)

4.9 Overdose

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 utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors,
ATC code: A02B C04

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. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

Anti-secretory Activity: After oral administration of a 20mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

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

Serum Gastrin Effects: In clinical studies patients were treated once daily with 10 or 20mg rabeprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection. In over 250 patients followed for 36 months of continuous therapy, no significant change in findings present at baseline was observed.
Other Effects: Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.

Clinical efficacy and safety
Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H. pylori* infection.

5.2 Pharmacokinetic properties
Absorption: Rabeloc is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20mg dose. Peak plasma concentrations (C_{max}) 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 affect the absorption of rabeprazole sodium.

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

Metabolism and excretion: Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolized through the cytochrome P450 (CYP450) hepatic drug metabolising system. *In vitro* studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these 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 ^{14}C 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: Adjusted 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 $\leq$ 5ml/min/1.73m^2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} 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 that 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 C_{max} to only 1.2-fold. 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 C_{max} 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 C_{max} had increased by only 40%.

5.3 Preclinical safety data

Non-clinical effects were observed 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol 25, Light Magnesium Oxide, Microcrystalline Cellulose, Starch (Dried), Hydroxy Propyl Cellulose(Klucel LF), Special Denatured Spirit, Carboxy Methyl Cellulose Calcium, Purified Talc, Magnesium Stearate, Collodial Silicon Dioxide, Hydroxy Propyl Methyl Cellulose (5 cps), Propylene Glycol, Purified Water, Methacrylic Acid Copolymer Dispersion, Polysorbate 80, Dibutyl Phthalate, Sodium Hydroxide, Ferric Oxide Yellow, Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

Alu/Alu blister pack of 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Cadila pharmaceuticals Limited,

1389, Trasad Road, Dholka,
Ahmedabad – 382225, Gujarat,
India

8. MARKETING AUTHORISATION NUMBER(S):

Rabeloc 10: 04720/07031/REN/2019
Rabeloc 20: 07988/08481/REN/2022

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