For the use of a Registered Medical Practitioner Only

RANTAC® R

℞ Rabeprazole Tablets IP 20 mg

COMPOSITION

Each enteric coated tablet contains:

Rabeprazole Sodium IP.....20 mg

Colours: Red Oxide of Iron & Titanium Dioxide IP

PHARMACEUTICAL FORM

Enteric Coated Tablet

THERAPEUTIC INDICATION

Indicated for the treatment of Gastroesophageal reflux disease (GERD),

duodenal ulcer & Zollinger elision syndrome.

DOSAGE AND ADMINISTRATION

Posology

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

Adults/elderly

Duodenal Ulcer: The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20 mg 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.

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

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease: 10 mg 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 10 mg 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 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

Method of administration: For oral use only.

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, 1 hour before a meal with some water.

CONTRAINDICATIONS

Hypersensitivity to the active substance, or to any of the excipients.

- Pregnancy and Breast feeding.

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. 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 20mg enteric coated tablets should not be chewed or crushed, but should be swallowed whole.

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 20mg enteric coated Tablets is first initiated in such patients. Co-administration of atazanavir with rabeprazole is not recommended.

Treatment with proton pump inhibitors, including rabeprazole, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and *Clostridium difficile*.

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 recognized 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.

Paediatric population: Rabeprazole tablet is not recommended for use in the children due to a lack of data on safety and efficacy. There have been post marketing reports of the blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative aetiology 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 aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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.

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. 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 10mg enteric coated Tablets 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 proton pump inhibitor treatment.

DRUG 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.

No interaction with liquid antacids was observed.

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 proton pump inhibitors. Therefore, PPIs, including rabeprazole, should not be co-administered with atazanavir.

USE IN SPECIAL POPULATION

Paediatric population: Rabeprazole tablets are not recommended for use in children due to a lack of data on safety and efficacy.

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

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 20mg enteric coated tablet is contraindicated during pregnancy.

Breastfeeding: 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 20mg enteric coated tablet must not be used during breast feeding.

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.

UNDESIRABLE EFFECTS

Proton Pump Inhibitors associated Acute Kidney Injury: Acute kidney injury has been reported with the use of Proton pump inhibitors (PPIs) including Pantoprazole, Omeprazole, lansoprazole, Esomeprazole, Rabeprazole etc.

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth.

The following adverse events have been reported from clinical trial and post-marketed experience. Frequencies are defined as: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data):

Infections and infestations: Common: Infection.

Blood and lymphatic system disorders: Rare: Neutropenia, Leucopenia, Thrombocytopenia, and Leucocytosis.

Immune system disorders: Rare: Hypersensitivity[1,2]

Metabolism and nutrition disorders: Rare: Anorexia. Not known: Hyponatremia, Hypomagnesaemia[4].

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: Not known: Peripheral oedema.

Respiratory, thoracic and mediastinal disorders: Common: Cough, Pharyngitis, and Rhinitis. Uncommon: Bronchitis, Sinusitis.

Gastrointestinal disorders: Common: Diarrhoea, Vomiting, and Nausea, Abdominal pain, Constipation, Flatulence, and Fundic gland polyps (benign). Uncommon: Dyspepsia, Dry mouth, Eructation. Rare: Gastritis, Stomatitis, Taste disturbance. Not known: Microscopic colitis.

Hepatobiliary disorders: Rare: Hepatitis, Jaundice, and Hepatic encephalopathy[3].

Skin and subcutaneous tissue disorders: Uncommon: Rash, Erythema[2]. Rare: Pruritus, Sweating, and Bullous reactions[2]. Very Rare: Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS). Not known: Subacute cutaneous lupus erythematosus[4].

Musculoskeletal and connective tissue disorders: Common: Non-specific pain, Back pain. Uncommon: Myalgia, Leg cramps, Arthralgia, and Fracture of the hip, wrist or spine[4].

Renal and urinary disorders: Uncommon: Urinary tract infection. Rare: Interstitial nephritis.

Reproductive system and breast disorders: not known: Gynecomastia. General disorders and *administration site conditions: Common:* Asthenia, Influenza like illness. Uncommon: Chest pain, Chills, and Pyrexia.

Investigations: Uncommon: Increased hepatic enzymes[3]. Rare: 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 tablets is first initiated in such patients.

[4] See Special warnings and precautions for use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

Experience to date with deliberate or accidental overdose 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 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.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Proton pump inhibitors.

Rabeprazole is a selective and irreversible proton pump inhibitor, suppresses gastric acid secretion by specific inhibition of the H+, K+ -ATPase, which is found at the secretory surface of parietal cells. In doing so, it inhibits the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen. 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.

Rabeprazole prevents the production of acid in the stomach. It reduces symptoms and prevents injury to the esophagus or stomach in patients with gastroesophageal reflux disease (GERD) or ulcers. Rabeprazole is also useful in conditions that produce too much stomach acid such as Zollinger-Ellison syndrome. Rabeprazole may also be used with antibiotics to get rid of bacteria that are associated with some ulcers.

PHARMACOKINETIC PROPERTIES

Absorption: Rabeprazole 20mg enteric-coated tablet is an Gastro-resistant tablet formulation. 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 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism.

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

Metabolism: Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised 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).

Excretion: Following a single 20 mg 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.

INCOMPATIBILITY

Not applicable.

PACKAGING INFORMATION

Strip of 10 Tablets.

STORAGE INSTRUCTIONS

Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

Tablet should be swallowed whole and not chewed or crushed.

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
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Worli, Mumbai - 400 030. India.

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Note: This prescribing information is applicable for India Market only.