For the use of a Registered Medical Practitioner only

℞ Rabeprazole Sodium Injection IP

Rabiet*

COMPOSITION:

Each vial contains:

Rabeprazole Sodium IP (Sterile) ..... 20 mg

PROPERTIES:

Dry Powder Injection

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, 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.

Pharmacodynamic Properties

Serum Gastrin Effects

In clinical studies patients were treated once daily with 10 or 20 mg 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.

During treatment with anti-secretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Pharmacokinetic properties

Absorption and Distribution

Absolute bioavailability rabeprazole I.V. is 100%. Rabeprazole is 96.3% bound to human plasma proteins.

Therapeutic Indications

For the short-term treatment of gastric and duodenal ulcers, gastro-oesophageal reflux disease (GERD), and as an alternative to oral therapy in patients who are unable to take oral proton-pump inhibitor (PPI).

POSOLOGY AND METHOD OF ADMINISTRATION:

I.V. administration is recommended only in cases where oral administration is not indicated. As soon as an oral therapy is possible, the I.V. therapy should be discontinued.

Recommended dose is I.V. administration of the content of one vial (20 mg Rabeprazole) once daily. Parenteral routes of administration other than I.V. are not recommended.

Injection: The content of the vial needs to be reconstituted with 5 ml Sterile Water for Injection and should be given slowly over 5–15 minutes.

Infusion: For I.V. infusion, the reconstituted solution should be further diluted and administered as a short-term infusion over 15–30 minutes.

Compatibility with Various I.V. Fluids

Rabeprazole I.V. is compatible with Sterile Water for Injection, and 0.9% Sodium Chloride Injection. No other

solvent or infusion fluid must be used for the administration of Rabeprazole I.V. injection.

Reconstitution

To reconstitute, add 5 ml of Sterile Water for Injection to make a solution. After preparation, the reconstituted solution must be used within 4 hours and the unused portion discarded. As with all parenteral admixtures, the reconstituted or further diluted solution should be examined for change in colour, precipitation, haziness or leakage. The unused portion should be discarded.

CONTRAINDICATIONS:

Rabeprazole Sodium for Injection is contraindicated in patients with a known hypersensitivity to Rabeprazole, substituted benzimidazoles or to any component of the formulation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Presence of Gastric Malignancy

Symptomatic response to therapy with Rabeprazole does not preclude the presence of gastric malignancy. Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *Helicobacter pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline, 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Interaction with Warfarin

Steady-state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased International Normalised Ratio (INR) and prothrombin time in patients receiving a PPI and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton-pump inhibitor (PPI) and warfarin concomitantly may need to be monitored for increases in the INR and prothrombin time.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs, including rabeprazole sodium. Acute inter- stitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersen-sitivity reaction. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Clostridium difficile-associated Diarrhoea

Published observational studies suggest that PPI therapy such as rabeprazole sodium may be associated with an increased risk of *C. difficile*-associated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

CDAD has been reported with the use of nearly all antibacterial agents.

Bone Fracture

Several published observational studies in adults 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, defined as multiple daily doses, 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 for osteoporosis-related fractures should be managed according to established treatment guidelines.

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including rabeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopaenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Rabeprazole sodium, discontinue the drug and refer the patient to the appro- priate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Cyanocobalamin (Vitamin B_{12}) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) 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 sodium.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Drugs Metabolised by CYP450

Rabeprazole is metabolised by the CYP450 drug-metabolising enzyme system. Studies in healthy subjects have shown that Rabeprazole does not have clinically significant interactions with other drugs metabolised by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single I.V. dose and phenytoin given as a single I.V. dose (with supplemental oral dosing). Steady-state interactions of Rabeprazole and other drugs metabolised by this enzyme system have not been studied in patients.

Warfarin

There have been reports of increased INR and prothrombin time in patients receiving PPIs, including Rabeprazole, and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and even death.

Cyclosporine

In vitro incubations employing human liver microsomes indicated that Rabeprazole inhibited cyclosporine metabolism with an IC50 of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of Rabeprazole This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Compounds Dependent on Gastric pH for Absorption

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds that are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with Rabeprazole. For example, in normal subjects, co-administration of Rabeprazole 20 mg q.d. resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and Cmax for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken con- comitantly with Rabeprazole. Co-administration of Rabeprazole and antacids produced no clinically relevant changes in plasma Rabeprazole concentrations.

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-marketing experience.

Frequencies are defined as follows: common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000) 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 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 Constipation Flatulence Fundic gland polyps (benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis
Hepatobiliary 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)	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip,wrist or spine[4]			
Renal and urinary disorders		Urinary tract infection	Tubulointerstitial nephritis (with possible progression to renal failure)		
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

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@jbpharma.com

FERTILITY, PREGNANCY AND LACTATION:

Pregnant Women

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.

Lactating Women

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 must not be used during breast feeding.

Paediatric Patients

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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 in 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.

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 utilised.

INCOMPATIBILITIES:

Rabeprazole I.V. is compatible with Sterile Water for Injection, and 0.9% Sodium Chloride Injection. No other solvent or infusion fluid must be used for the administration of Rabeprazole I.V. injection.

STORAGE:

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

PRESENTATION: 1 X 20 mg in 10 ml amber colour glass vial in a carton with 5ml SWFI ampoule along with pack insert.

Marketed by :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.
* Trade Mark under registration

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Note: This prescribing information is applicable for India Market only