RABICIP I.V. Injection (Rabeprazole sodium)

For the use of a Registered Medical Practitioner only

Qualitative And Quantitative Composition

Each vial contains:
Rabeprazole Sodium, ........20 mg

Dosage Form And Strength

Rabeprazole Sodium For intravenous (I.V.) administration only (20 mg)

Clinical Particulars

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, IP, and 0.9% Sodium Chloride Injection, IP. 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

RABICIP I.V. 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 interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity 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 appropriate 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 B₁₂) 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 Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at a 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.

Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Drug Interactions

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 IC_{50} 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 C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

The table below includes drugs with clinically important drug interactions and interactions with diagnostics when administered concomitantly with rabeprazole sodium and instructions for preventing or managing them.

Consult the labelling of concomitantly used drugs to obtain further information about interactions with PPIs.

**Clinically Relevant Interactions Affecting Drugs Co-Administered with Rabeprazole Sodium and Interactions with Diagnostics**

### Antiretrovirals

**Clinical Impact**

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

- Decreased exposure of some antiretroviral drugs (e.g. rilpivirine, atazanavir and nelfinavir) when used concomitantly with rabeprazole may reduce the antiviral effect and promote the development of drug resistance.
- Increased exposure of other antiretroviral drugs (e.g. saquinavir) when used concomitantly with rabeprazole may increase toxicity.
- There are other antiretroviral drugs that do not result in clinically relevant interactions with rabeprazole.

**Intervention**

- Rilpivirine-containing products: Concomitant use with rabeprazole sodium is contraindicated. See the prescribing information.
- Atazanavir: See the prescribing information for atazanavir for dosing information.
- Nelfinavir: Avoid concomitant use with rabeprazole sodium. See prescribing information for nelfinavir.
- Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.
- Other antiretrovirals: See the prescribing information.

### Warfarin

**Clinical Impact**

Increased INR and prothrombin time in patients receiving PPIs, including rabeprazole and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

**Intervention**

Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.

### Methotrexate
**Clinical Impact**  Concomitant use of rabeprazole with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of methotrexate with PPIs have been conducted.

**Intervention:** A temporary withdrawal of rabeprazole sodium may be considered in some patients receiving high-dose methotrexate administration.

**Digoxin**

**Clinical Impact**  Potential for increased exposure of digoxin.

**Intervention**  Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations.

**Drugs Dependent on Gastric pH for Absorption (e.g. iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole)**

**Clinical Impact**  Rabeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

**Intervention**  Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving rabeprazole sodium and MMF. Use rabeprazole sodium with caution in transplant patients receiving MMF.

**Combination Therapy with Clarithromycin and Amoxicillin**

**Clinical Impact**  Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions.

**Intervention**  See Contraindications and Warnings and Precautions in the prescribing information for clarithromycin.

**Tacrolimus**

**Clinical Impact**  Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

**Intervention**  Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.

**Interactions with Investigations of Neuroendocrine Tumours**

**Clinical Impact**  Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false-positive results in diagnostic investigations for neuroendocrine tumours.

**Intervention**  Temporarily stop rabeprazole sodium treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Secretin Stimulation Test

**Clinical Impact**  
Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.

**Intervention**  
Temporarily stop treatment with rabeprazole sodium at least 14 days before assessing to allow gastrin levels to return to baseline.

False-Positive Urine Tests for THC

**Clinical Impact**  
There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.

**Intervention**  
An alternative confirmatory method should be considered to verify positive results.

**Use in Special Populations**

Patients with Renal Impairment  
No dosage adjustment is necessary for patients with renal impairment.

Patients with Hepatic Impairment  
No dosage adjustment is necessary for patients with hepatic impairment.

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.

Geriatric Patients  
Of the total number of subjects (n=2,009) in clinical studies of rabeprazole sodium delayed-release tablets, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**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.

**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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection</td>
<td></td>
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<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropaenia Leucopaenia Thrombocytopaenia Leucocytosis</td>
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<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity\textsuperscript{1,2}</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
<td>Hyponatraemia Hypomagnesaemia \textsuperscript{4}</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Nervousness</td>
<td>Depression</td>
<td>Confusion</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache Dizziness</td>
<td>Somnolence</td>
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<tr>
<td>Eye disorders</td>
<td></td>
<td>Visual disturbance</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td>Peripheral oedema</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough Pharyngitis Rhinitis</td>
<td>Bronchitis Sinusitis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic gland polyps (benign)</td>
<td>Dyspepsia Dry mouth Eructation</td>
<td>Gastritis Stomatitis Taste disturbance</td>
<td>Microscopic colitis</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Hepatitis Jaundice Hepatic encephalopathy\textsuperscript{3}</td>
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</tr>
</tbody>
</table>

\textsuperscript{1}Hypersensitivity may be systemic, such as rash or angioedema, or local, such as pharyngitis or pericardial effusion.

\textsuperscript{2}Hypersensitivity reactions may occur in patients with a history of hypersensitivity to aspirin or other non-steroidal anti-inflammatory drugs.

\textsuperscript{3}Hepatitis may be self-limiting, mild, or severe with hepatic encephalopathy.

\textsuperscript{4}Hypomagnesaemia is a common occurrence following the administration of magnesium-based anti-emetics.
<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Rash</th>
<th>Pruritus</th>
<th>Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)</th>
<th>Sub-acute cutaneous lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Erythema²</td>
<td>bullous reactions²</td>
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<thead>
<tr>
<th>Musculoskeletal connective tissue and bone disorders</th>
<th>Non-specific pain</th>
<th>Myalgia</th>
<th>Arthralgia</th>
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</thead>
<tbody>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td>Fracture of the hip, wrist or spine⁴</td>
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<tr>
<th>Renal and urinary disorders</th>
<th>Urinary tract infection</th>
<th>Interstitial nephritis</th>
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<tr>
<th>Reproductive system and breast disorders</th>
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<th>Gynaecomastia</th>
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<tr>
<th>General disorders and administration site conditions</th>
<th>Asthenia</th>
<th>Influenza-like illness</th>
<th>Chest pain</th>
<th>Chills</th>
<th>Pyrexia</th>
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<tr>
<th>Investigations</th>
<th>Increased hepatic enzymes³</th>
<th>Weight increased</th>
</tr>
</thead>
</table>

1 Includes facial swelling, hypotension and dyspnea.

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 the treatment of patients with severe hepatic dysfunction, the prescriber is advised to exercise caution when treatment with rabeprazole 10 mg gastro-resistant tablets is first initiated in such patients.

4 See Special Warnings and Precautions for Use.

**Reporting of Suspected Adverse Reactions**

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

**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.

**Pharmacological Properties**

**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**

**Anti-Secretory Activity**

After oral administration of a 20 mg dose of rabeprazole sodium, the onset of the anti-secretory effect occurs within 1 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 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 3 days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

Decreased gastric acidity due to any means, including PPIs such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs 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 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.

Available published evidence suggests that PPIs should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

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 central nervous system (CNS), cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg 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.

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

**Pharmacokinetic Properties**

After oral administration of 20 mg rabeprazole, peak plasma concentrations ($C_{\text{max}}$) of rabeprazole occur over a range of 2.0 to 5.0 hours ($T_{\text{max}}$). The rabeprazole $C_{\text{max}}$ and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10–40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

**Absorption and Distribution**

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

**Metabolism**

Rabeprazole is extensively metabolized. The thioether and sulphone are the primar metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. \textit{In vitro} studies have demonstrated that rabeprazole is metabolized in the liver primarily by CYP450 3A (CYP3A) to a sulphone metabolite and CYP450 2C19 (CYP2C19) to desmethylrabeprazole. The thioether metabolite is formed non-enzymatically by reduction of rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3–5% of Caucasians and 17–20% of Asians). Rabeprazole metabolism is slow in these sub-populations; therefore, they are referred to as poor metabolizers of the drug.

**Elimination**

Following a single 20 mg oral dose of 14 C-labelled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the faeces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or faeces.

**Special Populations**

**Geriatric:** In 20 healthy elderly subjects, after oral administration of rabeprazole 20 mg once daily for 7 days, AUC values approximately doubled and the $C_{\text{max}}$ increased by 60% compared with values in a parallel younger control group. There was no evidence of drug accumulation after once-daily administration.

**Paediatric:** The pharmacokinetics of rabeprazole in paediatric patients under the age of 18 years has not been studied.

**Gender and Race:** In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and femalesubjects. In studies that used different formulations of rabeprazole, AUC$_{0-\infty}$ values for healthy Japanese men were approximately 50–60% greater than values derived from pooled data from healthy men in the United States.

**Renal Impairment:** In 10 patients with stable end-stage renal disease requiring maintenance haemodialysis (creatinine clearance: 2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared with 10 healthy volunteers.

**Hepatic Impairment:** In a single-dose study of 10 patients with chronic mild-to-moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC$_{0-24}$ was approximately
doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared with values in healthy men. In a multiple-dose study of 12 patients with mild-to-moderate hepatic impairment administered 20 mg rabeprazole once daily for 8 days, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ values increased approximately 20% compared with values in healthy age- and gender-matched subjects. These increases were not statistically significant. No information exists on rabeprazole disposition in patients with severe hepatic impairment.

### Non-Clinical Properties

#### Animal Toxicology or Pharmacology

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.

### Description

RABICIP I.V. contains rabeprazole sodium, which is a Proton Pump Inhibitor (PPI).

### Pharmaceutical Particulars

#### Incompatibilities

Data for incompatibility not available.

#### Shelf-Life

As on the pack.

#### Packaging Information

RABICIP I.V .........................Vial of 10 mL along with 5 mL Sterile Water for Injection, IP

#### Storage and Handling Instructions

Store below 30°C. Protect from light and moisture

### Patient Counselling Information

What is RABICIP I.V.?

RABICIP I.V. contains the active ingredient, rabeprazole sodium, in injection form. Rabeprazole act by reducing the amount of acid made by the stomach.

Do not take if you have an allergy to the drug

Do not take rabeprazole sodium if you

* Are allergic to rabeprazole sodium or any of the other ingredients of this medicine

Before you take this drug, tell your healthcare practitioner about other medications you may be taking

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important in case you are taking any of the following medicines:

* Atazanavir (used to treat HIV); it is not recommended to take Rabeprazole if you are taking atazanavir.
* Ketoconazole or itraconazole (used to treat infections caused by a fungus). Rabeprazole may lower the
amount of this type of medicine in your blood. Your doctor may need to adjust your dose
• Methotrexate (a chemotherapy medicine used in high doses to treat cancer) – if you are taking a high dose
dose of methotrexate, your doctor may temporarily stop your Rabeprazole treatment.
How should you take this medicine?
This medicine will be given by exactly as your doctor or pharmacist has told you. Check with your doctor or
pharmacist if you are not sure.
What are the possible side effects?
Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects
are usually mild and improve without you having to stop taking this medicine. If you notice any of the
following serious side effects, stop taking Rabeprazole and contact a doctor immediately, you may need
urgent medical treatment:
• Allergic reactions – the signs may include: sudden swelling of your face, difficulty breathing or low blood
pressure which may cause fainting or collapse.
• Frequent infections, such as a sore throat or high temperature (fever), or ulcers in your mouth or throat.
• Bruising or bleeding easily.
These side effects are rare (affect fewer than 1 in 1,000 people).
• Sudden onset of severe rash or blistering or peeling skin. This may be associated with a high fever and
joint pains (erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN))
These side effects are very rare (affect fewer than 1 in 10,000 people).
Other possible side effects: Common side effects (may affect up to 1 in 10 people):
• cough, sore throat (inflammation of the pharynx), runny nose.
• effects on your stomach or gut such as stomach pain, diarrhoea, wind (flatulence), feeling sick (nausea),
being sick (vomiting) or constipation
• aches, back pain, non-specific pain.
• weakness or loss of strength, flu like symptoms.
• difficulty sleeping.
• headache, dizziness.
• infection.
• benign polyps in the stomach.
Uncommon side effects (may affect up to 1 in 100 people):
• feeling nervous or drowsy.
• sleepiness.
• chest infection (bronchitis).
• painful and blocked sinuses (sinusitis).
• indigestion, dry mouth, belching.
• rash, skin redness (erythema).
• muscle pains, joint pains, leg cramps.
• bladder infection (urinary tract infection).
• chest pain, chills, fever.
• muscle, leg or joint pain.
• change in how your liver is working (which is measured by blood tests).
• fracture of the hip, wrist or spine.
Rare side effects (may affect up to 1 in 1,000 people):
• blood problems such as reduced number of white cells or platelets.
This can cause weakness, bruising or make infections more likely.
changes in white blood cells (show in blood tests) which may result in frequent infection.
allergic reactions including facial swelling, low blood pressure and breathing difficulties.
loss of appetite (anorexia).
depression.
visual disturbance.
upset stomach or stomach pain, sore mouth, taste disturbance.
inflammation of the liver, jaundice (yellowing of the skin or eyes).
itchy rash, sweating, skin blisters.
kidney inflammation (interstitial nephritis).
increased weight.

Not known (frequency cannot be estimated from the available data):

low levels of sodium in the blood which can cause tiredness and confusion, muscle twitching, fits and coma.
confusion.
swelling of the feet and ankles.
enlarged breasts in men.
Patients who have previously had liver problems may very rarely get encephalopathy (a brain disease).
rash, possibly with pain in the joints.
inflammation of the gut (leading to diarrhoea).

If you are on Rabeprazole for more than three months it is possible that the levels of magnesium in your blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate. If you get any of these symptoms, please tell your doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium. Do not be concerned by this list of side effects. You may not get any of them

How should I store this medicine?
Keep this medicine out of the sight and reach of children.
Store below 30°C. Protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

General information about the safe and effective use of this medicine.
Do not take rabeprazole sodium if you

• are pregnant or breastfeeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Rabeprazole if you

• have a stomach tumour.
• have or have had any liver problems.
• are taking a medicine called atazanavir (used to treat HIV).
• have reduced body stores or risk factors for reduced vitamin B12 and receive long term treatment with rabeprazole sodium. As with all acid reducing agents, rabeprazole sodium may lead to a reduced absorption of vitamin B12.
• are due to have a specific blood test (Chromogranin A).
• have ever had a skin reaction after treatment with a medicine similar to Rabeprazole that reduces stomach acid.

If you get a rash on your skin, especially in areas exposed to the sun, tell your doctor as soon as you can, as
you may need to stop your treatment with Rabeprazole. Remember to also mention any other ill-effects like pain in your joints. If you are not sure if any of the above applies to you, consult your doctor or pharmacist before taking Rabeprazole.

Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant disease. The possibility of stomach and oesophageal tumours should be excluded before the treatment is started.

If you take Rabeprazole on a long-term basis (longer than one year) your doctor will probably monitor you regularly. You should report any new or different symptoms whenever you see your doctor. Taking a proton pump inhibitor like Rabeprazole, especially over a period of more than one year, may slightly increase your risk of fracture of the hip, wrist or spine. Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis). Talk to your doctor straight away if you experience severe (watery or bloody) or persistent diarrhoea with symptoms such as fever, abdominal pain or tenderness, as rabeprazole has been associated with a small increase in infectious diarrhoea. Some abnormal blood and liver enzyme values have been reported during treatment with Rabeprazole. Usually, the values become normal when the treatment is discontinued. Children Rabeprazole are not recommended for use in children.

Pregnancy and breast-feeding Do not use Rabeprazole if you are pregnant or think you may be pregnant. Do not use Rabeprazole if you are breastfeeding or planning to breast-feed. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines Occasionally rabeprazole can cause sleepiness. Therefore, driving and operating machinery should be avoided if you are affected.

Any other information None.

Details Of The Manufacturer
Mfd. By Cipla Ltd.
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RABICIP I.V. Injection