RABICIP L Capsules (Rabeprazole sodium + Levosulpiride )

Composition

RABICIP L
Each hard gelatin capsule contains:
Rabeprazole Sodium, IP .......... 20 mg
(as enteric-coated pellets)
Levosulpiride ......................... 75 mg
(as sustained-release pellets)
Excipients .............................. q.s.

Dosage Form

Hard gelatin capsule

Pharmacology

Rabeprazole

Mechanism of Action
Rabeprazole sodium belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric PPI. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulphenamide. When studied in vitro, rabeprazole is chemically activated at pH 1.2, with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles, with a half-life of 90 seconds.

Antisecretory Activity
The antisecretory effect begins within 1 hour after oral administration of 20 mg rabeprazole sodium. The median inhibitory effect of rabeprazole sodium on 24-hour gastric acidity is 88% of maximal after the first dose. Rabeprazole sodium 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table below). This relatively prolonged pharmacodynamic action, compared with the short pharmacokinetic half-life (1-2 hours), reflects the
sustained inactivation of the H+, K+ATPase.

Table 1

Gastric acid parameters rabeprazole sodium versus placebo after 7 days of once-daily dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rabeprazole Sodium (20 mg q.d.)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Acid Output</td>
<td>0.4*</td>
<td>2.8</td>
</tr>
<tr>
<td>(mmol/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulated Acid Output</td>
<td>0.6*</td>
<td>13.3</td>
</tr>
<tr>
<td>(mmol/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Time Gastric pH&gt;3</td>
<td>65*</td>
<td>10</td>
</tr>
</tbody>
</table>

*(p <0.001 versus placebo)

Compared with placebo, rabeprazole sodium, 10 mg, 20 mg, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.

Table 2

AUC acidity (mmol/hr/l) rabeprazole sodium versus placebo on day 7 of once-daily dosing (Mean±SD)

<table>
<thead>
<tr>
<th>AUC Interval</th>
<th>Rabeprazole 10 mg</th>
<th>Rabeprazole 20 mg</th>
<th>Rabeprazole 40 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(hrs) (N=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08:00-13:00</td>
<td>19.6±21.5*</td>
<td>12.9±23*</td>
<td>7.6±14.7*</td>
<td>91.1±39.7</td>
</tr>
<tr>
<td>13:00-19:00</td>
<td>5.6±9.7*</td>
<td>8.3±29.8*</td>
<td>1.3±5.2*</td>
<td>95.5±48.7</td>
</tr>
</tbody>
</table>
After administration of 20 mg rabeprazole sodium tablets once daily for 8 days, the mean percent of time that gastric pH>3 or gastric pH>4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo (see table below). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole sodium tablets administered once daily for 8 days were compared with the same parameters for placebo, as illustrated below:

*(p <0.001 versus placebo)

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rabeprazole Sodium 20 mg q.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 8</td>
</tr>
<tr>
<td>Mean AUC&lt;sub&gt;0-24 hours&lt;/sub&gt;</td>
<td>340.8*</td>
<td>176.9*</td>
</tr>
<tr>
<td>Median trough pH (23 hours)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.77</td>
<td>3.51</td>
</tr>
<tr>
<td>% Time Gastric pH&gt;3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54.6*</td>
<td>68.7*</td>
</tr>
<tr>
<td>% Time Gastric pH&gt;4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44.1*</td>
<td>60.3*</td>
</tr>
</tbody>
</table>

<sup>a</sup>No inferential statistics conducted for this parameter.

<sup>b</sup>Gastric pH was measured every hour over a 24-hour period.

Effects on Oesophageal Acid Exposure
In patients with gastro-oesophageal reflux disease (GERD) and moderate-to-severe oesophageal acid exposure, rabeprazole sodium 20 mg and 40 mg tablets per day decreased 24-hour oesophageal acid exposure. After 7 days of treatment, the percentage of time that oesophageal pH < 4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving rabeprazole sodium 20 mg and in 100% of subjects receiving rabeprazole sodium 40 mg. With rabeprazole sodium 20 mg and 40 mg per day, significant effects on gastric and oesophageal pH were noted after 1 day of treatment, and more pronounced after 7 days of treatment.

Effects on Serum Gastrin
In patients given daily doses of rabeprazole sodium for up to 8 weeks to treat ulcerative or erosive oesophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease, the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

In a group of subjects treated daily with rabeprazole sodium 20 mg tablets for 4 weeks, a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of cytochrome (CY) P2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

Effects on Enterochromaffin-like (ECL) Cells
Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females.

In over 400 patients treated with rabeprazole sodium tablets (10 or 20 mg/day) for up to 1 year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the PPI. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumours observed in rats.

Endocrine Effects
Studies in humans for up to 1 year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with rabeprazole sodium for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 beta-oestradiol, thyroid-stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6beta-hydroxycortisol, serum testosterone, and circadian cortisol profile.

Other Effects
In humans treated with rabeprazole sodium for up to 1 year, no systemic effects have been observed on the central nervous, lymphoid, haematopoietic, renal, hepatic, cardiovascular or respiratory systems. No data are available on long-term treatment with rabeprazole sodium and ocular effects.

Microbiology
The following in vitro data are available but the clinical significance is unknown.
Rabeprazole sodium, amoxicillin and clarithromycin as a three-drug regimen has been shown to be active against most strains of Helicobacter pylori in vitro and in clinical infections

H. pylori
Susceptibility testing of H. pylori isolates was performed for amoxicillin and clarithromycin using the agar dilution
methodology, and minimum inhibitory concentrations (MICs) were determined.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Incidence of Antibiotic-Resistant Organisms among Clinical Isolates

Pre-treatment Resistance

Clarithromycin pre-treatment resistance rate (MIC ≥1 μg/mL) to *H. pylori* was 9% (51/560) at baseline in all treatment groups combined. A total of >99% (558/560) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤0.25 μg/mL) to amoxicillin at baseline. In 2 patients, baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL were seen.

For susceptibility testing information about *H. pylori*, see the Microbiology section in the prescribing information for clarithromycin and amoxicillin.

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**Table 4**

<table>
<thead>
<tr>
<th>Days of RAC Therapy</th>
<th>Clarithromycin Pre-treatment Results</th>
<th>Total Number</th>
<th><em>H. pylori</em>-Negative (Eradicated)</th>
<th><em>H. pylori</em>-Positive (Persistent)</th>
<th>Post-Treatment Susceptibility Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>S  b</td>
<td>I  b</td>
<td>R  b</td>
</tr>
<tr>
<td>7</td>
<td>Susceptible b</td>
<td>129</td>
<td>103</td>
<td>2 0 1 23</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Intermediate b</td>
<td>0</td>
<td>0</td>
<td>0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Resistant b</td>
<td>16</td>
<td>5</td>
<td>2 1 4 4</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Susceptible b</td>
<td>133</td>
<td>111</td>
<td>3 1 2 16</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Intermediate b</td>
<td>0</td>
<td>0</td>
<td>0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>

  b Susceptible (S) MIC ≤0.25 μg/mL, Intermediate (I) MIC = 0.5 μg/mL, Resistant (R) MIC ≥1 μg/mL

RAC = rabeprazole plus amoxicillin and clarithromycin

  a Includes only patients with pre-treatment and post-treatment clarithromycin susceptibility test results.
Patients with persistent *H. pylori* infection following rabeprazole, amoxicillin and clarithromycin therapy will likely have clarithromycin resistant clinical isolates. Therefore, clarithromycin susceptibility testing should be done when possible. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

**Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

In the US multicentre study, a total of >99% (558/560) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤0.25 μg/mL) to amoxicillin at baseline. The other 2 patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL, and both isolates were clarithromycin-resistant at baseline; in one case, *H. pylori* was eradicated. In the 7- and 10-day treatment groups, *H. pylori* was eradicated in 75% (107/145) and 79% (112/142), respectively, of the patients who had pre-treatment amoxicillin-susceptible MICs (≤0.25 μg/mL). No patients developed amoxicillin-resistant *H. pylori* during therapy.

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**Levosulpiride**

Levosulpiride is a prokinetic agent that increases the lower oesophageal sphincter pressure more rapidly and effectively than other therapeutic agents. The prokinetic effect of levosulpiride is mediated through the blockade of enteric dopamine D₂ receptors.

Levosulpiride also acts as a moderate agonist at the 5-HT4 receptor. The serotonergic (5-HT4) component of levosulpiride may enhance its therapeutic efficacy in gastrointestinal disorders (helping reduce nausea and vomiting). This property, together with antagonism at D₂ receptors, may contribute to its gastrointestinal prokinetic effect.

The drug also exerts clinical anti-depressant effects/anti-psychotic effects by blocking the presynaptic dopaminergic D₂ receptors.

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**Pharmacokinetics**

Rabeprazole sodium delayed-release capsules are enteric-coated to allow rabeprazole sodium, which is acid-labile, to pass through the stomach relatively intact.

After oral administration of 20 mg rabeprazole, peak plasma concentrations (Cₘₐₓ) of rabeprazole occur over a range of 2.0 to 5.0 hours (Tₘₐₓ). The rabeprazole Cₘₐₓ 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.

Absolute bioavailability for a 20 mg oral capsule of rabeprazole (compared with intravenous administration) is approximately 52%. When rabeprazole sodium capsules are administered with a high-fat meal, the Tₘₐₓ is variable; concomitant food intake may delay the absorption up to 4 hours or longer. However, the Cₘₐₓ and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus, rabeprazole sodium capsules may be taken without regard to timing of meals.
Rabeprazole is 96.3% bound to human plasma proteins.

Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic non enzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome (CY) P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *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 desmethyl rabeprazole. 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.

Following a single 20 mg oral dose of 14C-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 tablets 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 was studied in paediatric patients with GERD, aged 12 to 16 years.

Patients, 12 to 16 Years of Age: The pharmacokinetics of rabeprazole was studied in 12 adolescent patients (12 to 16 years of age) with GERD, in a multicentre study. Patients received rabeprazole 20 mg tablets once daily for 5 or 7 days. An approximate 40% increase in exposure was noted following 5-7 days of dosing compared with the exposure after 1-day dosing. Pharmacokinetic parameters in adolescent patients with GERD, 12 to 16 years of age, were within the range observed in healthy adult volunteers.

Gender and Race

In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. 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 ≤5 mL/min/1.73 m²), 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, AUC_{0-infinity} and C_{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. Please refer to DOSAGE AND ADMINISTRATION for information on dosage adjustment in patients with hepatic impairment.

Combined Administration with Antimicrobials
In 16 healthy volunteers genotyped as extensive metabolizers with respect to CYP2C19, 20 mg rabeprazole sodium, 1,000 mg amoxicillin, 500 mg clarithromycin, or all three drugs were administered in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and C_{max} for clarithromycin and amoxicillin were not different following combined administration compared with values following single administration. However, the rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, following combined administration. The AUC and C_{max} for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

Concomitant Use with Clopidogrel
Clopidogrel is metabolized to its active metabolite, in part, by CYP2C19. A study of healthy subjects, including CYP2C19 extensive and intermediate metabolizers receiving once-daily administration of clopidogrel 75 mg concomitantly with placebo or with rabeprazole sodium 20 mg (n=36), for 7 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio was 88%, with 90% CI of 81.7-95.5%) when rabeprazole sodium was co-administered, compared with administration of clopidogrel with placebo.

Levosulpiride
Oral bioavailability is about 30%; peak plasma concentrations occur after about 3 hours. Excretion mainly via urine. Plasma half-life: 9.7 hours (oral); 4.3 hours (I.V.).

Indications
- Healing of erosive or ulcerative gastro-oesophageal reflux disease (GERD)
- Maintenance of healing of erosive or ulcerative GERD
- Healing of duodenal ulcers
- Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome
- Irritable bowel syndrome
- Chronic gastritis

Dosage And Administration
One capsule per day on an empty stomach.

Contraindications
RABICIP L capsules are contraindicated in patients with a known hypersensitivity to rabeprazole or levosulpiride or to any component of the formulation.
Warnings And Precautions

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 *H. 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.

Concomitant Use with Warfarin

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

*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 hospitalized 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. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with rabeprazole sodium, refer to the WARNINGS AND PRECAUTIONS sections of those package inserts.

Bone Fracturb

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.
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.

Concomitant Use of Rabeprazole Sodium 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.

Drug Interactions

Rabeprazole

*Drugs Metabolized by CYP450*

Rabeprazole is metabolized by the CYP450 drug-metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized 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 metabolized 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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.

Concomitant use of atazanavir and PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

**Drugs Metabolized by CYP2C19**

In a clinical study in Japan evaluating rabeprazole in adult patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared with extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

**Combined Administration with Clarithromycin**

Combined administration consisting of rabeprazole, amoxicillin and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin.

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs.

**Methotrexate**

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at a 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.

**Clopidogrel**

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of rabeprazole sodium.

**Levosulpiride**

Reduced bioavailability with sucralfate, aluminium- and magnesium-containing antacids. Effect on gastrointestinal motility may be antagonized by anticholinergic agents, narcotics and analgesics. Avoid alcohol.

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**Pregnancy**

There are no adequate and well-controlled studies in pregnant women.

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**Lactation**

There are no adequate and well-controlled studies in nursing mothers.
Undesirable Effects

Rabeprazole

Worldwide, over 2,900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment.

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience

Adults

The data described below reflect exposure to rabeprazole sodium in 1,064 adult patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in adult patients with erosive or ulcerative GERD, duodenal ulcers and gastric ulcers. The population had a mean age of 53 years (range, 18-89 years) and had a ratio of approximately 60% male: 40% female. The racial distribution was 86% Caucasian, 8% African-American, 2% Asian, and 5% other. Most patients received 10 mg, 20 mg or 40 mg/day of rabeprazole sodium.

An analysis of adverse reactions appearing in ≥2% of rabeprazole sodium patients (n=1,064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs 1%), pharyngitis (3% vs 2%), flatulence (3% vs 1%), infection (2% vs 1%), and constipation (2% vs 1%).

Three long-term maintenance studies consisted of a total of 740 adult patients; at least 54% of adult patients were exposed to rabeprazole for 6 months and at least 33% were exposed for 12 months. Of the 740 adult patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg of rabeprazole sodium, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.

The safety profile of rabeprazole in the maintenance studies in adults was consistent with what was observed in the acute studies.

Other adverse reactions seen in controlled clinical trials, which do not meet the above criteria (≥2% of rabeprazole sodium treated patients and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: headache, abdominal pain, diarrhoea, dry mouth, dizziness, peripheral oedema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Combination Treatment with Amoxicillin and Clarithromycin:

In clinical trials using combination therapy with RAC, no adverse reactions unique to this drug combination were observed. In the US multicentre study, the most frequently reported drug-related adverse reactions for patients who received RAC therapy for 7 or 10 days were diarrhoea (8% and 7%) and taste perversion (6% and 10%), respectively.

No clinically significant laboratory abnormalities particular to the drug combinations were observed.

For more information on adverse reactions or laboratory changes with amoxicillin or clarithromycin, refer to their
respective package prescribing information, under the ADVERSE REACTIONS section.

Paediatric
In a multicentre, open-label study of adolescent patients, 12 to 16 years of age, with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to rabeprazole sodium that occurred in ≥2% of 111 patients were headache (9.9%), diarrhoea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study that were not previously observed in adults.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of rabeprazole sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: sudden death; coma, hyper-ammonaemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angio-oedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; TSH elevations; bone fractures; hypomagnesaemia and C. difficile-associated diarrhoea. In addition, agranulocytosis, haemolytic anaemia, leucopenia, pancytopenia and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

Levosulpiride
Levosulpiride was well tolerated; the incidence of adverse events, though not negligible, were mostly mild and treatment discontinuation was infrequent. The most common adverse events were drowsiness/sedation and endocrine effects. Other side effects may include the following:

- Acute muscular dystonia characterized by abnormal movements (twitching, tremor, etc.) of the hands, leg, tongue and facial muscles.
- Increase in plasma prolactin levels manifested by breast enlargement, production of milk, and stopping of menstrual periods. This can be taken care of with the use of lower dose of this drug.
- Neuroleptic malignant syndrome (characterized by muscle rigidity, suggestive of muscle damage).
- Akathisia (uncontrollable desire to move about without any anxiety).
- Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of the face, mouth and jaw.
- Weight gain.

Overdosage
There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole q.d.

No specific antidote for rabeprazole is known. Rabeprazole is extensively protein-bound and is not readily dialysable. In
the event of overdosage, treatment should be symptomatic and supportive.

### Storage And Handling Instructions

Protect from light and moisture. Store below 25°C.

### Packaging Information

RABICIP L: Strip pack containing 10 capsules

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### RABICIP L Capsules

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