SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICAL PRODUCT

(Rabeprazole sodium for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Rabeloc IV:

Rabeprazole Sodium for Injection 20 mg

Each Vial contains:

Rabeprazole Sodium	20 mg
Excipients	q.s.

3. PHARMACEUTICAL FORM:

Lyophilized sterile powder for Injection

The active ingredient in Rabeprazole Sodium for Injection is Rabeprazole Sodium for injections, a substituted benzimidazoles that inhibits gastric acid secretion. Rabeprazole Sodium is known chemically as 2-[[[2-(3-methoxypropoxy)-3-methyl-2-methyl-2-pyridinyl]-methyl]sufinyl]-1H-benzimidazole sodium salt.

It has an empirical formula of $C_{18}H_{20}NaO_3S$ and molecular weights of 381.43.

Rabeprazole Sodium is white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in Ethanol, Chloroform and Ethyl Acetate and insoluble in Ether and n-Hexane. The reconstituted solution of Rabeprazole Sodium for Injection with sterile water for Injection BP has pH in the range of 8.5 to 5.

Dissolution:

Rabeprazole Sodium for Injection gives clear colourless solutions on reconstituted with 5 ml Sterile Water for Injections.

Compatibility with various IV fluids:

Rabeprazole Sodium for Injection is compatible with Dextrose Injections, Dextrose Saline Injection.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Intravenous rabeprazole is indicated for the treatment of:

1. Active duodenal ulcer with bleeding or severe erosions.
2. Active / Benign gastric ulcer with bleeding or severe erosions.
3. Severe erosive or ulcerative gastro-esophageal reflux diseases (GORD/GERD) or Non-erosive Reflux Diseases [NERD].

4. Prevention of Acid-Aspiration during Surgery
5. Stress-induced mucosal injury in clinical care, e.g. head-injury, burns, MI, etc.
6. Sequential-therapy [Step-Up] therapy from oral Rabeprazole, e.g. a patient previously on Oral Rabeprazole who is temporarily unable to take oral Rx for any reason, e.g. during a surgical procedure.[1]
7. Any condition where patient is unable to take oral PPIs.
8. Prevention of Pulmonary Acid Aspiration During Surgery

4.2 Posology and method of administration:

Dosage and Administration**:**
Use by the indication of treating physician.
Parenteral rabeprazole is only used when the oral form is not appropriate and it should be changed to the oral route as soon as possible

Dosage
No dosage adjustment is necessary for patients with renal or hepatic impairment or old age. No need to adjust dose in patients with haemodialysis

Dosage of over 40mg/day has not yet been studied in patients with hepatic impairment. No need to adjust dose in patients with haemodialysis.

Recommended dose for adults: 20 mg rabeprazole given once daily by intravenous bolus injection or by intravenous infusion for 7 to 10 days.

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

IV PPIs are used in the following indications:

- Upper GI Bleeds
- Severe GERD (Gastro Esophageal Reflux Disease), where the patient is unable to take orally.
- Stress – induced mucosal injury.
- Pre-anesthetic suppression of acid-secretion.
- Prevention of Pulmonary Acid Aspiration During Surgery

Oral PPIs are primarily used in the following indications:

- GERD & Reflux Esophagitis
- Gastric Ulcer (GU)
- Duodenal Ulcer (DU)
- ZES (Zollinger Ellison Syndrome)
- H-pylori eradication.

As would be expected IV acid suppression is therefore used in more severe case, where a higher degree of acid-suppression is required.

To just use one example:
Pantoprazole orally - used at 40 mg once daily for GERD.
IV Pantoprazole – used at 80 mg per 24 hours (40 mg bolus followed by infusion @ 6-8 mg per hr. up to maximum of 120 mg per day.

Thus in spite of a bioavailability of 77%, the IV drug is administered in severe indications at double the conventional oral dosage.
Dose-defining data generated by Dr. Rupesh Mehta:[1]

- Patients with acute bleeding peptic ulcers after successful endoscopic haemostasis were enrolled in pilot studies (N = 5 each).
- They were given an intravenous bolus injection of 10, 20 or 40 mg of escalating doses of IV Rabeprazole.
- Symptoms of signs were evaluated continuously every hour over 48 hours and then on a need-to-measure basis for the next seven days.
- The symptoms used were: Pain, heartburn, nausea/ vomiting, odynophagia/ dysphagia.
- Compared with the infusion with 10 mg Rabeprazole, the infusion of 20 mg Rabeprazole showed a faster normalization of the symptoms and a greater percentage of time that patient had relief from symptoms.

Based upon this dose defining study, clinical trials were undertaken on 103 patients using 20 mg per day dosage at prestigious centres across India.
These trials have also been slated for presentation at reputed international conferences such as:

1. The UEGW: United European Gastroenterology Week, Sept 2004
2. The Asia Pacific Digestive Week, Oct 2004, Beijing.

The investigators concluded that IV Rabeprazole 20 mg once daily was safe & highly effective in the management of:

I) Upper gastrointestinal Bleeding
II) Severe GERD (Gastro Esophageal Reflux Disease), where the patient is unable to take any therapy or PPI orally.
III) Stress – induced mucosal injury.
IV) Pre-anesthetic acid suppression.
V) Prevention of Pulmonary Acid Aspiration During Surgery

Conclusion:

20 mg once daily is going to be used in the above mentioned critical conditions as a treatment or as a corrective therapy

10 mg once or twice daily is likely to be used as a prophylactic or preventive therapy to prevent the onset of the above mentioned conditions. Furthermore, some doctors may also prefer to split 20 mg dosage as 10 mg twice daily.

Hence it is necessary to launch both 10 & 20 mg formulation of IV Rabeprazole.
In managing patients with bleeding peptic ulcers, prevention of rebleeding is a particular challenge to haemostasis and fibrinolysis, both of which involve reactions that are impaired in acidic gastric environment. Therefore, such patients are expected to benefit from profound acid suppression. The present investigation aimed to establish a safe and, with regard to pH elevation, effective treatment that based on in vitro evidence, should provide clinical benefit in this patient population.

METHODS: Patients with acute bleeding peptic ulcers (Forrest Ia, Ib, IIa) after successful endoscopic haemostasis were enrolled in two pilot studies (N = 20 each). They were given an intravenous bolus injection of 80 mg of pantoprazole immediately followed by continuous infusion of either 6 mg/h or 8 mg/h pantoprazole for 72 h. Intragastric pH was measured continuously over 24 h and, if possible, for up to 48 h.

RESULTS: Intragastric pH increased rapidly to values of about 6 with both treatments. For the 0-24 h period, the median pH values were 6.1 (68% range 4.5-7.4) and 6.1 (68% range 5.2-6.7) in patients receiving 6 mg/h and 8 mg/h continuous infusion, respectively; the values for the 0-48 h period were 5.9 (4.9-6.7) and 6.3 (5.5-7.0), respectively. The median percentage time that pH was > or =6 during the 0-48 h interval was 47% (68% range 28-89) for the 6 mg/h treatment group and 64% (68% range 41-84) for the 8 mg/h treatment group. Both treatment regimens with pantoprazole were well tolerated based on electrocardiographic measurements, vital signs, clinical laboratory values, and adverse events.
Compared with the infusion with 6 mg/h pantoprazole, the continuous infusion of 8 mg/h pantoprazole showed a lower inter individual variability of the intragastric pH and a greater percentage of time that pH was >/ or =6. Thus, with regard to safety and efficacy, an initial 80-mg bolus injection, followed by 8 mg/h continuous infusion, seems to be the adequate treatment in patients with a high risk of rebleeding.[2]

4.3 Contra-indication:

- Patients with known hypersensitivity to rabeprazole sodium substituted benzimidazoles or to any Excipients used in the formulations
- Pregnancy and lactation

4.4 Special warnings and special precautions for use:

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

Although no evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic imperilments versus normal age and sex matched controls, the prescribers is advised to excursive caution when treatment with rabeprazole is fist initiated in patients with severe hepatic dysfunctions.[1]

The extent of rabeprazole concentrations increases by old age, poor metabolizer's status for CYP2C19 and impairment of liver function is not greater than two-fold, impairment renal function doses not affect the elimination. Even in patients with delayed elimination, no relevant accumulation of rabeprazole was observed upon long-term administration. In in-vivo studies, rabeprazole had no noteworthy effect on the metabolism of other drugs. [1]

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

Children:
It is not recommended for use in children, as there is little experience of its use in this group.

4.5 Interactions with other medications and other forms of interactions:

Rabeprazole is metabolized by the cytochrome P450 (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 intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC50 of 62 micromolar, a concentration that is over 50 times higher than the Cmax 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.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which 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 QD 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 concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.[1]

4.6 Pregnancy and Lactation:

Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from Rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

There are no data on the safety of rabeprazole in human pregnancy.

4.7 Effects on ability to drive and use machines:

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

4.8 Undesirable effects:

Intravenous Rabeprazole has been studied in clinical trials in several populations including patients having GERD with a history of erosive esophagitis, patients with Zollinger-Ellison Syndrome and healthy subjects.

Adverse experiences occurring in of patients treated with intravenous Rabeprazole in clinical trials are shown below by body system. In most instances, the relationship to Rabeprazole was unclear.[1]

BODY AS A WHOLE: Headache, injection site reaction.
DIGESTIVE SYSTEM: Constipation, Diarrhea.
NERVOUS SYSTEM: Insomnia.
RESPIRATORY SYSTEM: Rhinitis.

The following is a list of possible side-effects that may occur from all constituting ingredients of Rabeloc IV Injection. This is not a comprehensive list. These side-effects are possible, but do not always occur. Some of the side-effects may be rare but serious.

Consult your doctor if you observe any of the following side-effects, especially if they do not go away.

The following undesired events, listed by body system, have been reported with the following frequencies: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

Nervous system disorder

Common: Insomnia, Dizziness, Headache

Rare: Sleepiness

Respiratory, thoracic and mediastinal disorder

Common: Cough, Pharyngitis, Rhinitis

Rare: Bronchiitis and Sinusitis

Gastrointestinal Disorder

Common: Abdominal pain, Constipation, Flatulence, Diarrhoea, Vomiting, Nausea

Rare: Dyspepsia, Gastritis

General disorder and administration site condition

Common: Asthenia, Influenza like illness

Uncommon: Chest pain, Fever, Chills

Skin and subcutaneous tissue disorder

Uncommon: Rash, Erythema

Rare: Pruritus, sweating, Bullous reaction

Oropharyngeal Disorder

Rare: Pharyngitis

Mucoskeletal and connective tissue disorder

Common: Back pain, Nonspecific pain

Uncommon: Myalgia, Leg cramps, arthralgia

Infections and infestations

Rare: Flu syndrome, Infection, Bronchitis, Urinary tract infection

Cardiac Disorders

Rare: Chest pain

Psychiatric Disorders

Very Rare: Stress, Depression, Sadness

Eye Disorder

Very Rare: Visual disturbances,

Blood and lymphatic system disorder

Rare: Leucopaenia, Thrombocytopenia, Neutropenia, Leucocytosis

Investigation

Uncommon: Weight gain, Elevated liver enzymes
Rare: weight increased

Head-to-head comparative studies between Rabeprazole I.V. for Injection and oral Rabeprazole other proton pump inhibitors (oral or I.V.), or H_2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the email ID: Safety.cadila.global@cadilapharma.co.in

4.9 Overdose:

There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage 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 QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.[1,3]

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

5.1.1 Mechanism of actions:

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-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 proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. 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. [4,5]

5.1.2 Specific Pharmacological actions:

5.1.2.1 Antisecretory activity:

The anti-secretory effect begins within one hour after oral administration of 20 mg rabeprazole. The median inhibitory effect of rabeprazole on 24 hour gastric acidity is 88% of maximal after the first dose. Rabeprazole 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 to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H^+ , K^+ ATPase.

Compared to placebo, rabeprazole 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. [6]

After administration of 20 mg rabeprazole once daily for eight 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 administered once daily for eight days were compared to the same parameters for placebo. [5]

Another study conducted by CPL suggests use in Prevention of Pulmonary Acid Aspiration during Surgery, Each patient was administered either 20 mg dose of IV Rabeprazole or identical placebo, before surgery within 60 to 90 minutes prior to the scheduled induction of anesthesia. In this randomized, double-blind, placebo control, multicenter, clinical trial, IV Rabeprazole 20 mg produced a significantly higher mean pH level than the placebo as well as significantly less mean volume of gastric contents following administration prior to the surgery.

None of the patients in the study had any episode of pulmonary aspiration of gastric contents. Hence, IV Rabeprazole, when administered 90-120 minutes prior to surgery is envisaged to reduce the number of patients “at risk” for pulmonary aspiration (pH < 2.5 and volume < 25 ml) in patients undergoing surgery under general anaesthesia. Better result was observed in terms of per cent patients at risk (0%) of aspiration with IV Rabeprazole, compared to the results observed by Nishina et al, and Hussain et al.

Both treatments were well tolerated by the patients. No statistically significant difference was established for AEs between both the study treatments. No significant abnormality in the laboratory investigations, physical examination and vital signs was observed. The result of the present study establishes that the administration of 20 mg dose of IV Rabeprazole before elective surgery, is effective in reducing risk of acid aspiration and provided adequate prophylaxis for the acid aspiration syndrome in elective surgery patients under GA.

In view of the higher pH, reduced gastric volume and favorable safety profile, the IV Rabeprazole along with pre-anesthetic medication, provides adequate prophylaxis for acid aspiration and prevention of pulmonary acid aspiration during surgery in patient under general anesthesia and is expected to provide better safety and efficacy for the same in the actual clinical and surgical setting.

5.1.2.2 Gastric Acid Parameters:

Compared to placebo, Rabeprazole 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.

After administration of 20 mg Rabeprazole Sodium once daily for eight 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 administered once daily for eight days were compared to the same parameters for placebo.

5.1.2.3 Gastric Acid Parameters:

Effects on Serum Gastrin:

In patients given daily doses of Rabeprazole Sodium for up to eight weeks to treat ulcerative or erosive esophagitis 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.

5.1.2.4 Effects on Esophageal Acid Exposure:

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, Rabeprazole 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH<4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.0%, respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH>4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving Rabeprazole 20 mg and in 100% of subjects receiving Rabeprazole 40 mg. With Rabeprazole 20 mg and 40 mg per day, effects on gastric and esophageal pH were significant and substantial after one day of treatment, and more pronounced after seven days of treatment.

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, rabeprazole 20 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH<4 decreased from baselines of 24.7% to 5.1% respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH>4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving rabeprazole 20 mg. With rabeprazole 20 mg per day, effects on gastric and esophageal pH were significant and substantial after one day of treatment, and more pronounced after seven days of treatment.

In the another pharmacodynamic studies in *H. pylori*-negative volunteers support the earlier data and show rabeprazole to have greater antisecretory effects over a 24-hour period than esomeprazole, omeprazole, lansoprazole and pantoprazole. A crossover study in 18 volunteers measured 24-hour intragastric pH. Rabeprazole 20mg was found to have a similar onset of action to pantoprazole 40mg (1.75h for both drugs) and omeprazole 20mg (1.5h) but

a slower onset than lansoprazole 30mg ; however, rabeprazole was the most effective acid inhibitor during the first 24 hours ($p < 0.05$ *vs* comparators).

Two studies have compared rabeprazole with omeprazole 20 mg/day show rabeprazole to have a similar or faster initial onset of action and a significantly higher antisecretory effect on day 1, over a 24-hour period, than omeprazole. Rabeprazole 20 mg/day and omeprazole 20 mg/day had similar onsets of action (3 to 4 *vs* 2 to 3h) and produced similar inhibition of acidity at 3 hours in an 8-day placebo-controlled trial in 23 healthy volunteers; however, the degree of inhibition with rabeprazole but not omeprazole continued to increase to a maximum 87% at 7 hours. [15] The 24-hour acidity on day 1 was significantly improved with rabeprazole compared with omeprazole ($p < 0.001$). Median inhibition by rabeprazole was 88% and by omeprazole it was 42% of steady-state inhibition measured on day 8. In a study among 24 healthy volunteers, percent inhibition of gastric acid secretion was significantly greater with rabeprazole than omeprazole at both days 1 and 8 (day 1: 64 *vs* 38%, $p < 0.01$; day 8: 64 *vs* 50%, $p < 0.03$).[7]

5.1.2.5 Antibacterial Activity against *Helicobacter pylori:*

Rabeprazole is significantly more effective than esomeprazole in increasing gastric pH on the first day of treatment. In a crossover study 24 volunteers were randomised to receive either rabeprazole or esomeprazole 20 mg/day for 5 days. [17] On day 1 the percentage of time that the pH was >3 and >4 was longer for rabeprazole than for esomeprazole ($p = 0.001$) and in addition the area under the intragastric pH curve from 0 to 24 hours was higher for rabeprazole than esomeprazole ($p < 0.005$).

The effects of rabeprazole on acid secretion appear to be of long duration (=24h).In 12 volunteers, *H. pylori* status unknown, who were randomised to rabeprazole 20 mg/day or placebo for 14 days, acid secretion did not recover completely during the 72 hours after drug administration ceased. [18] The half-time for restoration of acid secretion was >48 hours after 7 days' administration of rabeprazole 5 to 40 mg/day in 38 *H. pylori*positive individuals.

In review literature[2] the range of minimum inhibitory concentrations (MICs) of rabeprazole against *H. pylori* was considerably lower than that seen for omeprazole *in vitro*.[2] The ranges of MICs were 0.063 to 1 mg/L for rabeprazole, 0.031 to 4 mg/L for the thioether metabolite of rabeprazole, 0.25 to 2 mg/L for lansoprazole and 0.5 to 16 mg/L for omeprazole in a study assessing 133 clinical isolates.[9-10]

The motility of *H. pylori* allows it to colonise the gastric mucosa; *in vitro* rabeprazole and its thioether metabolite were shown to inhibit the motility of this bacteria. In a study in seven clinical isolates of *H. pylori* the MIC for 50%of strains was 0.25, 16, 16 and >64 mg/L for the thioether metabolite of rabeprazole, rabeprazole, lansoprazole and omeprazole,

respectively. [9] Rabeprazole and omeprazole to induce CYP isoenzymes. [7] The study concluded that rabeprazole may have a lower potential for causing CYP mediated.

5.1.3 General Pharmacological actions:

5.1.3.1 Effects on Serum Gastrin level:

In patients given daily doses of rabeprazole for up to eight weeks to treat ulcerative or erosive esophagitis 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.

5.1.3.2 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 (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats. [11]

5.1.3.3 Endocrine Effects:

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

5.1.3.4 Other Effects:

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

5.2 Pharmacokinetic properties:

The rabeprazole C_{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 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours. [6]

In a randomized, balanced open-label, two period, two treatment, two way cross over study in 28 health male and female volunteers, the pharmacokinetics (PK) of 20 mg intravenous rabeprazole was compared with 20 mg oral rabeprazole. The PK parameters are listed below:

PK parameter	Oral 20 mg (N=26) #	Intravenous (N=28)
Cmax (ng/ml) [a]	441 ± 216	1646 ± 461
Tmax (hours) [a]	4.2 ± 1.2	0.1 ± 0.1
T1/2 (hours) [b]	1.5 ± 0.8	1.0 ± 0.6
AUC0-∞ (ng*hr/ml) [a]	709 ± 319	1290 ± 357
AUC0-24 (ng*hr/ml) [a]	689 ± 318	1280 ± 357

Two subjects had no detectable levels of rabeprazole after oral administration

[a] p value is 0.0001

[b] p value is 0.0122

Statistically significant treatment differences were observed for all PK parameters.

In another study, a total of 63 subjects (33 males and 30 females) were recruited at four research centers and given a 5-day therapeutic course of rabeprazole (10, 20, or 40 mg) administered as single daily doses during a 30-minute period. The PK parameters on Day 1 and Day 5 are listed below:

Pharmacokinetic parameters for the three dose groups following the administration of a single dose on the first day and repeated daily doses on the fifth day of rabeprazole by intravenous infusion over a 30-min period for 5 days

Dose group	**Timea (day)**	**AUC(0-τ) (mg·min/L)**	**AUC(0-∞) (mg·min/L)**	**Cmax (μg/mL)**	**t½ (min)**	**MRT(0-τ)**	**Cltotal (L/min)**	**Vd (L/kg) (min)**
Low (10 mg)	Day 1	51.9±22.1	55.5±26.3	0.64±0.11	71.9±42.0	83.0± 20.4	0.22±0.08	0.33± 0.13
	Day 5	59.3±23.9	62.7±27.3	0.76±0.15	68.3±29.5	81.0± 18.7	0.19±0.07	0.28± 0.08
Middle (20 mg)	Day 1	96.7±27.6	103.4±30.9	1.30±0.26	60.1±16.4	78.1± 12.7	0.21±0.07	0.30± 0.08
	Day 5	106.7±27.8	109.9±30.4	1.39±0.25	61.1±18.3	75.1± 12.6	0.20±0.07	0.28± 0.11
High (40 mg)	Day 1	188.4±65.8	213.3±87.7	2.6± 0.54	68.3±16.6	77.5± 16.3	0.22±0.05	0.34± 0.10
	Day 5	200.3±79.0	238.0±91.5	2.91±0.53	73.3±25.8	77.6± 14.7	0.20±0.05	0.31± 0.11

Values are given as the mean ± SD

AUC, Mean area under the plasma concentration–time curve:

AUC(0-τ), AUC over a dosing interval at steady-state;

AUC(0-∞), AUC for time 0 to infinity;

Cmax, peak plasma level; t½, elimination half-life of drug;

MRT, mean retention time; Cltotal, total clearance; Vd, volume of distribution
a Day 1 and Day 5 denote the first and fifth day of rabeprazole infusion, respectively

5.3 Preclinical safety data:

Rabeprazole is a substituted benzimidazoles proton pump inhibitors. It inhibits H^+/ K^+ -ATPase activity on the surface of gastric parietal cells and thus blocks the final steps of the gastric acid secretion. Its pharmacological activities where characterised in a number of *in vitro* and *in vivo* preparations.

Rabeprazole sodium, a potent pump inhibitor, inhibits gastric acid secretion by inhibiting the H^+/K^+-ATPase, the final step of gastric acid secretion, with IC_{50} of ~2.0-2.6 $\times 10^{-7}$ M in porcine gastric parietal cells. It was demonstrated that rabeprazole interacts with SH-groups on the inner part and surface of the enzyme, which undergoes conformational change & then leads to the inhibition of the enzyme activity. Its desmethyl metabolite (M_3) also inhibits the activity of H^+/K^+-ATPase with IC_{50} of 2.9×10^{-7} M. It was also demonstrated that (±)-rabeprazole (racemic mixture), R- (+)-rabeprazole [R-(+) enantiomer], and S-(-)-rabeprazole [S-(-) enantiomer] are equipotent in inhibiting the H^+/ K^+ ATPase in procaine gastric parietal cells. Rabeprazole was demonstrated to inhibit gastric acids secretion in rats, rabbits and dogs. Rabeprazole inhibits cAMP –induced acid secretion in the isolated rabbit gastric glands with histamine-induced gastric acid secretion with ID_{50} of 1 mg/kg. The ID_{50} of rabeprazole for inhibition of histamine-induced gastric acid secretion in dogs was 0.06 mg/kg. both thioether (M1, 2 mg/kg) and desmethyl (M3, 0.5 mg/kg) metabolites inhibit histamine induced gastric acid secretion in dogs by 41% and 47% at 1 hour after dosing. These results suggest that rabeprazole is therapeutically useful in the diseased conditions such as GERD, gastric and duodenal ulcers and pathological hypersecretory conditions.

In general, the plasma concentration of rabeprazole was increased with dose. Its oral bioavailability was variable since rabeprazole is unstable in gastric juice. The oral bioavailability can be improved by pretreatment with sodium bicarbonate buffer or delivering directly into the duodenum or using the enteric coated tablets. For example, in rats, the bioavailability following oral dose of rabeprazole was ~ 11-21% while the bioavailability following intraduodenal administration of rabeprazole was ~ 37-91%. In humans, the oral bioavailability of enteric-coated tablets was 52 %. After oral administration, C_{max} was reached within 5 min in mice and rats and ~8-11 min in dogs. Rabeprazole was quickly declined following i.v. and oral administration with half life of ~ 6-10 minutes in rats, 24 minutes in dogs and 42-90 minutes in humans. Rabeprazole was oxidized at the position of sulfoxide to sulfone rabeprazole or reduced to the thioether-metabolism of rabeprazole and its sulfone metabolite is mediated by CYP3A form of the human cytochrome P450 enzyme while the conversion of rabeprazole to desmethyl metabolite is mediated by CYP2C19 form. Thioether rabeprazole in the major metabolite identified in the human plasma. Very low levels of M2 were also detected in the human plasma. Both M1 and M3 were detected in the mouse, rats and dog plasmas. The carboxylic

acid derivative was the major metabolite identified in the mouse, rats and dog urine. M6 was also a major metabolite in the dog feces and bile. Mercapturic acid (M5) was also found in the urine of the rat and dog. The des-methyl metabolite (M3) is pharmacologically active with similar potency to the parent compound. The tissue distribution studies indicated that the highest radioactivity was detected in the thyroid followed by the liver, gastric mucosa, bone marrow and pituitary gland in the rats. The highest radioactivity was detected in the bile followed by eye, liver, stomach and kidney in dogs. The volume of distribution was similar in dogs (~0.4 L/kg) and in humans (0.34 L/kg). In rats the volume of distribution is ranged from 0.37 L/kg to 1.17 L/kg. The total clearance was 0.23 L/hr/kg in humans and ~ 0.6-0.7 L/hr/kg in dogs and ~6-60 L/hr/kg in rats. Rabeprazole was highly bound to plasma proteins in the humans (96.2-98.6) and rats and dogs (91.4-93.3%). The major route of excretion was by the urine and feces in mice, rats and dogs. The radioactivity was recovered in the feces (42-50%in mice, 46-53% in the rats and 53% in the dogs) and urine (20-23% in mice, 39-44% in rats and 33% in dogs). In humans, ~ 90% of the drug is excreted in the urine, mainly as mercapturic acid and carboxylic acid.

Single oral doses of Rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs

In a 88/104-week carcinogenicity study in CD-1 mice, Rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to Rabeprazole (AUC) of 1.40 μg•hr/mL which is 1.6 times the human exposure (plasma AUC $_{0\text{-(infinity)}}$ = 0.88 μg•hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to Rabeprazole (AUC) of about 0.1 μg•hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a Rabeprazole plasma exposure (AUC) of about 0.2 μg•hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/-) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Teratogenic Effects. **Pregnancy Category B:** Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to Rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women.

Following intravenous administration of ^{14}C-labeled Rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized Rabeprazole is excreted in human breast milk. Administration of Rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m ^{2}) resulted in decreases in body weight gain of the pups.

Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from Rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. PHARMACETICAL PARTICULARS

6.1 List of Excipients:

Mannitol, Sodium hydroxide, water for injection

6.2 Incompatibility:

Not applicable

6.3 Shelf-life:

24 Months

6.4 Special precautions for storage:

Store below 25°C. Protect from light

6.5 Nature and contents of containers:

Rabeloc IV: 5ml vial packed in a carton.

6.6 Instructions for use and handling:

Not applicable.

7. MARKETING AUTHORISATION HOLDER:

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1389, Trasad Road, Dholka – 385 225,
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