## 1.3 Product Information

### 1.3.1 Summary of Product Characteristics (SmPC)

**1. Name of the medicinal product**

SAL RABEPRAZOLE, Rabeprazole Sodium for Injection 20 mg

**2. Qualitative and Quantitative composition**

Each vial contains:
Rabeprazole Sodium
eq. to Rabeprazole 20 mg (Lyophilised)
Excipient q.s

**3. Pharmaceutical Form**

Sterile Lyophilised powder for injection

**4. Clinical Particulars**

**4.1 Therapeutic Indications**

Rabeprazole Sodium for Injection is an alternative in patients for whom oral administration of rabeprazole is not indicated.
Rabeprazole Sodium for Injection is indicated in the treatment of the following:

1. Sequential-therapy (step-up) from oral rabeprazole, e.g. a patient previously on oral rabeprazole who is temporarily unable to take oral medication for any reason.
2. Active duodenal ulcer with bleeding or severe erosions.
3. Active gastric ulcer with bleeding or severe erosions.
4. Short-term treatment of erosive or ulcerative GERD
5. Prevention of acid aspiration.
6. Stress-induced mucosal injury in critical care.
7. Pathological hypersecretory conditions, including Zollinger-Ellison syndrome

**4.2 Posology and method of administration**

The IV administration is recommended only in cases where oral administration is not indicated. As soon as an oral therapy is possible the IV therapy should be discontinued.
Recommended dose is IVadministration of the content of one vial (20 mg rabeprazole) once daily.
Parenteral routes of administration other than IV are not recommended.

Injection:
The content of the vial needs to be reconstituted with 5 ml sterile water for injection, which should be given slowly over 5-15 minutes.

Infusion:
For IV 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 Sodium for Injection is compatible with sterile water for injection and 0.9% sodium chloride injection. No other solvent or infusion fluid must be usedfor administration of Rabeprazole Sodium for 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 theunused portion discarded. As with all parenteral admixtures, the reconstitutedor further diluted solution should be examined for change in colour, precipitation, haziness or leakage. The unused portion should be discarded.

## 4.3 Contraindications

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

## 4.4 Special warning and precaution 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 *H.pylori* infection (221of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with H. pylori infection at baseline (105 of 326 patients) had mildor moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric bodytended 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 intestinalmetaplasia 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*-associateddiarrhoea (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 sections of those package inserts.

**Bone Fracture**
Several published observational studies in adults suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of thehip, 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 orlonger). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosisrelatedfractures 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 3months, in most cases after a year oftherapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacementand 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 andprolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporarywithdrawal of the PPI may be considered in some patients.

## 4.5 Interaction with other medicinal products and other forms of interaction

**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 $IC_{50}$ 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 occurdue to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg q.d. resulted inan 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 noclinically 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 atazanavirplasma 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 suppressionwas 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 poormetabolizers 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 druginteractions, 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 metabolitehydroxy methotrexate. 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 ofclopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of rabeprazole sodium.

## 4.6 Pregnancy and Lactation

**Pregnant Women:**
The safety of rabeprazole sodium treatment in pregnancy has not been established. Rabeprazole should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus.

**Nursing Women:**
It is not known whether rabeprazole is excreted in human milk. Rabeprazole should not be given to nursing mothers unless the expected benefits outweigh the potential risks to the infant.

## 4.7 Effects on the ability to drive and use machines

Based on the pharmacodynamic properties and the adverse event profiles, it is unlikely that Rabeprazole sodium for injection 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

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.

**Adult:**
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.

**Paediatric**
In a multicenter, open-label study of adolescent patients, 12 to 16 years of age, with a clinical diagnosis of symptomatic GERD or endoscopically provenGERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to rabeprazole sodium thatoccurred 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 reportedadverse reactions that occurred in ≥2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study thatwere not previously observed in adults.

**Post marketing Experience**
The following adverse reactions have been identified during post-approval use of rabeprazole sodium. Because these reactions are reported voluntarily from apopulation 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 havebeen reported.

## 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 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.

## 5. Pharmacological Particulars

### 5.1 Pharmacodynamic properties

ATC code: A02BC

Therapeutic class: Proton pump inhibitor

Rabeprazole sodium belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamineH2-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 1hour 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%.

This relatively prolonged pharmacodynamic action, compared with the short pharmacokinetic half-life (1-2 hours), reflects the sustained inactivation of the H+, K+ATPase.

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.

After administration of 20 mg rabeprazole sodium tablets once daily for 8days, 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. The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole sodium tablets administered once daily for 8days were compared with the same parameters for placebo.

**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 7days of treatment, the percentage of time that oesophageal 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 intra-oesophageal 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 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 1day of treatment, and more pronounced after 7days of treatment.

**Effects on Serum Gastrin**

In patients given daily doses of rabeprazole sodium for up to 8weeks 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 1year, 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 tumors observed in rats.

**Endocrine Effects**

Studies in humans for up to 1year 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 1year, 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 vitrodata* 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.

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 notpossible, alternative antimicrobial therapy should be instituted.

Amoxicillin Susceptibility Test Results and Clinical / Bacteriological OutcomesIn the US multicenter 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 amoxicillinat 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 atbaseline; 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* duringtherapy.

## 5.2 Pharmacokinetic properties

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). Therabeprazole 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 areadministered 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 tohuman plasma proteins.

**Metabolism**
Rabeprazole is extensively metabolized. 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 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 7days, AUC values approximately doubled and the Cmax 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 18years 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. Instudies that used different formulations of rabeprazole, $AUC_{0\text{-infinity}}$ values forhealthy Japanese men were approximately 50-60% greater than values derivedfrompooled 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, $AUC_{0\text{-}24}$ 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 impairmentadministered 20 mg rabeprazole once daily for 8days, $AUC_{0\text{-infinity}}$ 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.

## 5.3 Pre-clinical Safety

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 20 mg/day) was found to have no effect on fertility and reproductive performance of male and female rats.

# 6. Pharmaceutical Particulars

## 6.1 List of Excipients

Mannitol
Sodium Hydroxide

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf Life**
24 months
Use the reconstituted solution within one hour.

**6.4 Special Precautions for storage**
Protect from light and moisture. Store below 30°C.

**6.5 Nature and contents of container**
Rabeprazole sodium for Injection is packed in 10 ml amber tubular glass vial with 20 mm grey bromobutyl rubber stopper and 20 mm aluminium coloured flip off seal. Sealed vial is labeled and packed in carton along with the package insert.

**6.6 Special precautions for disposal and other handling**
No Special precautions for disposal and other handling required

**7. Marketing Authorization Holder**
**SAKAR HEALTHCARE LIMITED**
Block No. 10-13, Sarkhej-Bavla Highway,
Changodar, Ahmedabad - 382213, Gujarat, India

**8. Marketing Authorization Number**
Will be included after marketing authorization

**9. Date of first Authorization /renewal of the authorization**
Will be included after marketing authorization

**10. Date of revision of text**
Will be included after marketing authorization