Rabeprazole Sodium for Injection 20 mg

RABICIP I.V.

COMPOSITION
Each vial contains
Rabeprazole sodium .....20 mg
As sterile freeze-dried powder for reconstitution with 5 ml of sterile water for injection IP

PHARMACOLOGY
Pharmacodynamics
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.

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% .This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1–2 hours) reflects the sustained inactivation of the H^+/K^+ ATPase.

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, significant effects on gastric and esophageal pH were noted after one day of treatment, and more pronounced after seven days of treatment.

Effects on Serum Gastrin
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.

In a group of subjects treated daily with rabeprazole 20 mg 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 CYP2C19 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 (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.

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 β-estradiol, 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 6β-hydroxycortisol, serum testosterone and circadian cortisol profile.

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.

Pharmacokinetics
After oral administration of 20 mg rabeprazole, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (T_{max}). 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 is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

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

Metabolism
Rabeprazole is extensively metabolized. The thioether and sulphone are the 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 cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 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 to 5% of Caucasians and 17 to 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-labeled 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 feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

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

Pediatric: The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years has not been studied.

Gender and Race: In analysis 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-∞ 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 hemodialysis (creatinine clearance 2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 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 to 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 eight days, AUC 0-∞ and C_{max} values increased approximately 20% compared to 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.

INDICATIONS
Rabeprazole I.V. is an alternative in patients for whom oral administration of rabeprazole is not indicated.

Rabicip I.V. is indicated in the treatment of:

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 gastroesophageal reflux disease (GERD)
5. Prevention of acid-aspiration.
6. Stress-induced mucosal injury in critical care.
7. Pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

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

Infusion: For intravenous infusion the reconstituted solution should be further diluted and administered as short-term infusion over 15-30 min.

Compatibility with various I.V. fluids
Rabeprazole I.V. is compatible with sterile water for injection I.P. and 0.9% sodium chloride injection I.P. **No other solvent or infusion fluid must be used for administration of rabeprazole I.V. injection.**

Reconstitution

To reconstitute add 5 ml of sterile water for injection to make a solution.

After preparation, the reconstituted solution must be used within 4 hours and the unused portion discarded. As with all parenteral admixtures, the reconstituted or further

diluted solution should be examined for change in colour, precipitation, haziness or leakage .The unused portion should be discarded.

pH of the reconstituted solution : Between 11.2-12.5.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

WARNINGS AND PRECAUTIONS

Bone Fracture

Several published observational studies suggest that proton pump inhibitor (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 the established treatment guidelines.

Drug interactions

Drugs metabolized by CPY450

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). 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 proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in 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 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 C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored

when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors 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 patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to 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.

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.

Renal impairment
No dose adjustment is necessary in patients with renal impairment

Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation
Since many drugs are excreted in milk, caution should be exercised when rabeprazole is administered to a nursing mother.

Pediatric use
The safety and effectiveness of rabeprazole in pediatric patients has not been established.

Geriatric use
No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

UNDESIRABLE EFFECTS
Worldwide, over 2900 patients have been treated with oral 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.
An analysis of adverse reactions appearing in ≥ 2% of oral rabeprazole patients and with greater frequency than placebo, revealed the following adverse reactions: pain, pharyngitis, flatulence, infection, and constipation Other adverse reactions that were seen in controlled clinical trials which do not meet the above criteria (≥2% of rabeprazole treated patients and > placebo) and for which there is a possibility of a causal relationship to rabeprazole include the following: headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Postmarketing Reports
Musculoskeletal: bone fracture

OVERDOSAGE
There has been no experience with large overdoses of rabeprazole. 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.

STORAGE AND HANDLING INSTRUCTIONS
Store below 25°C.
Protect from light.

PACKAGING INFORMATION
RABICIP-I.V. is available in a vial of 10 ml with 5 ml sterile water for injection IP

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