PERMITTED DAILY EXPOSURE FOR RABEPRAZOLE SODIUM

1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Rabeprazole Sodium have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Rabeprazole is a medication that decreases stomach acid. It is used to treat peptic ulcer disease, gastroesophageal reflux disease and excess stomach acid production such as in Zollinger–Ellison syndrome. It may also be used in combination with other medications to treat Helicobacter pylori. Effectiveness is similar to other proton pump inhibitors (PPIs). It is taken by mouth.

Common side effects include constipation, feeling weak, and throat inflammation. Serious side effects may include osteoporosis, low blood magnesium, Clostridium difficile infection, and pneumonia. Use in pregnancy and breastfeeding is of unclear safety. It works by blocking H+/K+-ATPase in the parietal cells of the stomach.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Rabeprazole sodium is a white to yellowish white crystalline powder and exhibits polymorphism. It is soluble in water. pH is between 10.0 and 12.0 in 1% w/v in water. pKa is 8.9.

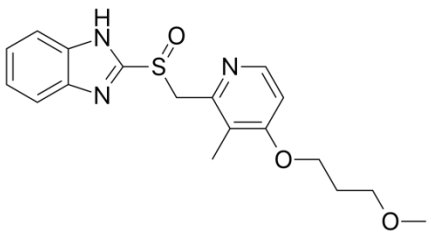
IUPAC name: (RS)-2-([4-(3-Methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl)-1H-benzo[d]imidazole

Chemical Abstract Services (CAS) Registry Number: 117976-89-3

Molecular Weight: 359.44 g·mol−1

Chemical Formula: $C_{18}H_{21}N_3O_3S$

Molecular Structure:



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4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	-	√	-

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	
Pharmacokinetics data	Pharmacokinetics Rabeprazole sodium tablets are enteric-coated. Absorption is rapid following ingestion. After oral administration of 20 mg Rabeprazole sodium, peak plasma concentrations (Cmax) are reached at an average of 1.6-5.0 hours; bioavailability compared to intravenous administration is 52%. Rabeprazole does not accumulate and its pharmacokinetics are not altered by multiple dosing. The plasma half-life is approximately one hour. **Absorption:** Following oral administration, Rabeprazole is rapidly absorbed and can be detected in plasma as early as 0.5 hours. The Rabeprazole C_{max} and AUC are linear with doses from 10 mg to 40 mg. Taking Rabeprazole sodium tablets with food does not alter C_{max} or AUC relative to the fasting state; the Tmax is increased by 1.7 hours. Antacids do not significantly affect the absorption of Rabeprazole sodium. Administration of Rabeprazole sodium with a high fat meal may delay its absorption by approximately 4 hours or longer; however, the C_{max} and the extent of absorption (AUC) are not altered. **Distribution:** Rabeprazole is 96.3% bound to human plasma proteins **Metabolism:** In humans the thioether and carboxylic acid are the main plasma metabolites. These metabolites were not observed to have significant antisecretory activity. The sulphone, desmethyl-thioether and mercapturic acid conjugate minor metabolites were observed at lower levels. Only the desmethyl metabolite has a small amount of antisecretory activity, but it is not present in plasma. In vitro studies have demonstrated that Rabeprazole is metabolized primarily by non-enzymatic reduction to form the thioether metabolite. Rabeprazole is also metabolized in the liver by cytochromes P450 3A (CYP3A), to a sulphone metabolite, and cytochrome P450 2C19 (CYP2C19), to desmethyl 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. **Excretion:** Following a single 20 mg 14C-labelled oral dose of Rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as two metabolites: a mercapturic acid conjugate and a carboxylic acid; there are also two unknowns. The remainder of the dose was recovered in feces.

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Acute (Single-Dose) Toxicity Studies of Rabeprazole and its metabolites, synthetic by-products, degradation products, and enantiomers were conducted in mice, rats and/or dogs. The oral LD50 in mice and rats was ≥1000 mg/kg; the intravenous LD50 in mice and rats was ≥150 mg/kg. Clinical signs consisted of laboured breathing, prostration, salivation, mydriasis, convulsions, and death. In dogs, the oral lethal dose was >2000 mg/kg. Clinical signs at oral doses of 400 and 2000 mg/kg included watery diarrhea, tonic convulsions, emesis, salivation, and prostration. There was no delayed toxicity in these acute studies.

Species/ Strain (Status)	Number/ Gender/ Group	Route of Admin./ Vehicle	Dose	Duration	LD50 or NOEL	
Mouse/ICR (Oral route: fasted 19-22 hrs prior to dosing; IV route: ad libitum feeding	5 per sex per group	PO (gavage)/ purified water IV/ physiological saline	**Male:** 629, 786, 983, 1229, 1536, 1920 and 2400 mg/kg **Female:** 629, 786, 983, 1229, 1536, 1920, 2400 and 3000 mg/kg **Male:** 131, 164, 205, 256, and 320 mg/kg **Female:** 164, 205, 229, 256, and 320 mg/kg	Single dose	1206 220	1012 237
Rat/Slc: SD (oral route: fasted 17-24 hrs prior to dosing; IV route: ad libitum feeding)	5 per sex per group	PO (gavage)/ purified water IV/ physiological saline	**Male:** 819, 1024, 1280, 1431, 1600 and 2000 mg/kg **Female:** 655, 819, 1024, 1280, 1600 and 2000 mg/kg **Male:** 98, 123, 154, 172 and 192 mg/kg **Female:** 98, 123, 154, 192, 240 and 300 mg/kg	Single dose	1447 157	1322 152
Rat Slc:SD (ad libitum feeding)	5 per sex per group	IV/NaOH and physiological saline	0, 50, 100, and 200 mg (S-) E3810*/kg 50, 100, and 200 mg (R+) E3810*/kg	Single dose	Not Determined	Not Determined
Rat/Slc: SD (animals were fasted overnight)	5 per sex per group	Degradation Products I and II and Impurity PO (gavage) Metabolite IV/ 0.5 methylcellulose solution	Degradation Prod. I: 0, 500, and 1500 mg/kg Degradation Prod. II: 50, 150, and 500 mg/kg Impurity: 500 and 1500 mg/kg Metabolite: 0, 10, 30 mg/kg (male and female), 100 mg/kg (male only)	Single dose	Not Determined	Not Determined
Dog/Beagle (ad libitum feeding)	1 per sex per group	PO (gavage)/ purified water	80, 400, and 2000 mg/kg	Single dose	>2000	>2000

Repeated Dose Toxicity (Chronic Toxicity)

Case Study 1: In the 5-week juvenile rat study (282 male and 282 female, Study 900948), Sprague Dawley rat from Days 7 to 41 post-partum were exposed to 5, 25, or 150 mg/kg Rabeprazole by oral gavage for 5 weeks. Treatment increased the serum gastrin concentrations and stomach weight. Histopathological examination revealed a dose related increase of cytoplasmic eosinophilia of chief cells in gastric mucosa. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg or higher and females at 25 mg/kg or higher. The changes were reversible. **The NOAEL of the 5-week study in rats was 25 mg/kg.**

Case Study 2: In the 90-day oral toxicity study in neonatal dogs, Rabeprazole was given by oral gavage to 7 days old dogs (31 male and 32 female Beagle dog pups) at 0, 3, 10, and 30 mg/kg/day (Study 900949). Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration /necrosis of parietal cells and mucosal hypertrophy/hyperplasia at the fundus of the stomach in a dose-related manner. The changes were reversible. **The NOAEL of the 90 day study in dogs was**

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SUMMARY OF HAZARD IDENTIFICATION:	
	3 mg/kg. **Case Study 3:** In a previous 104-week carcinogenicity study in Sprague-Dawley rats, Rabeprazole at 5 mg/kg/day induced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats. At the same dose level, Rabeprazole also induced ECL cell carcinoid tumors in female rats (Aciphex label). **Case Study 4:** Long-Term (Repeat-Dose) Toxicity Studies of Rabeprazole Sodium was studied in mice, rats and dogs after oral and intravenous administration. **Case Study 5:** Mice received oral doses of 2-400 mg/kg for up to 104 weeks. In mice, signs of toxicity (most evident in male mice) at 400 mg/kg included torpor, ataxia, hypopnea, bradypnea, and prostration. These signs resolved within 30 minutes. Increases in stomach and/or liver weight, thickening of the gastric glandular mucosa and/or hyperplastic gastropathy were observed at doses of 25, 100 and 400 mg/kg. It was concluded that oral doses up to 200 mg/kg (dose reduced to 100 mg/kg at week 41) for 88 weeks in males and 104 weeks in females did not provide any evidence of an oncogenic potential. A number of changes in the stomach that were attributable to the pharmacological activity of Rabeprazole sodium were seen in animals treated with 200 mg/kg (dose reduced to 100 mg/kg at week 41). **Case Study 6:** Rats received oral doses ranging from 1-300 mg/kg for up to 13 weeks and intravenous doses 1- 75 mg/kg up to four weeks. In the rat, Rabeprazole sodium was well tolerated in all dose groups (5, 15, 30, 60 and 120 mg/kg [females only]) when administered by gavage for six months, as morphologic changes were slight in magnitude and were not associated with alterations in growth, morbidity or mortality. Drug-related changes were detected in the kidney, thymus, stomach and/or thyroid at doses >15 mg/kg. No effects were observed at 5 mg/kg. In a 52-week study of rats administered doses of 1, 5 and 25 mg/kg by gavage, the gastric changes observed in the treated animals were attributable to the expected pharmacological effects and not toxicological changes, and the NOAEL was 5 mg/kg. Intravenous administration of Rabeprazole sodium in the rat at doses of 75 mg/kg for 14 days showed clinical signs such as hypoactivity, salivation, prone position, and flushing of the nose, but these signs disappeared after one hour of administration. Thymus weight was decreased and liver weight was increased. **Case Study 7:** Dogs received oral doses 0.1-30 mg/kg up to one year and intravenous doses 1-25 mg/kg up to 14 days. Rabeprazole Sodium had no effect on liver, kidney, heart, or lung at doses up to and including 30 mg/kg given by oral administration. Because of the smaller thymus weights observed in females treated with 30 mg/kg, the NOEL was 10 mg/kg. Rabeprazole Sodium (0.1, 0.3, or 1.0 mg/kg) and omeprazole (0.3, 1.0, or 3.0 mg/kg) were given orally to male and female dogs for 13 weeks followed by a 13-week recovery period. Expected pharmacologic responses (elevated gastrin levels and gastric changes) were observed with both proton pump inhibitors. Gastric changes were reversible at 0.3 mg/kg with both compounds and no gastric lesions were detected at 0.1 mg/kg of Rabeprazole Sodium. Effects were not observed in other organ systems with either compound. In a one-year followed by a two-month reversibility phase study, soft and watery stools and

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SUMMARY OF HAZARD IDENTIFICATION:	
	emesis were among the observations made in dogs treated with 8 or 25 mg/kg Rabeprazole sodium. Changes in clinical chemistry parameters included increases in cholesterol and triglycerides, and decreases in chloride and total protein. Serum gastrin levels, gross and histopathologic changes in stomach including increases in stomach weight, gastric mucosal and non-mucosal mass, and ECL hypertrophy and/or hyperplasia were observed in the Rabeprazole treated groups. The maximum tolerated dose was 8 mg/kg and the NOEL was 2 mg/kg. In a 52-week study, a number of changes were observed in the stomach of dogs treated with 1 or 5 mg/kg of Rabeprazole Sodium. These changes included increased stomach weight, thickening of the gastric mucosa, chief cell cytoplasmic atrophy, foci of cellular and chromogranin positive cell hypertrophy, and elevated gastrin levels. These changes, considered to be the result of a prolonged pharmacological effect and not a toxic effect of Rabeprazole Sodium, were completely or partially reversed at the end of the recovery period. In a 52-week study, over a dose range of 0.2 to 5 mg/kg, no change in ECL cell populations was evaluated. In a 14-day study in the dog, Rabeprazole was administered intravenously at doses of 1, 5 and 25 mg/kg. The lowest dose tested (1 mg/kg) was judged to be a no-effect-dose level for toxicity for Rabeprazole in this study. At daily doses of 5 mg/kg, treatment-related findings included vomiting and stool changes and histopathologic changes in the thyroid and the stomach. **Pharmacologically Mediated Effects:** In repeat-dose studies of up to one year in duration in rats and dogs and a three-month study in mice, trophic changes in the gastric mucosa were expected based on experience and the published literature of the H2-receptor antagonists and other proton pump inhibitors (Abe-1990, Ekman-1985, Hakanson-1986&1992, Atkinson-1990, Tuch-1992, Betton-1988, Creutzfeldt1986, Poynter-1985&1991, Havu-1986&1990, Polak-1988). Gastric changes, stimulated by chronic and sustained acid suppression, were manifested by hypergastrinemia, ECL-cell hypertrophy, hyperplasia, and neoplasia (female rats only), chief cell eosinophilia, and fundic mucosal thickening in rats. Gastric changes were observed at low doses in these studies: 1 mg/kg-rat, 0.3 mg/kg-dog, 25 mg/kg-mouse. Increases in gastrin levels and trophic effects on the gastric mucosa were not observed at 0.2 mg/kg in a 52-week dog study. A four-week study in antrectomized rats treated with 40 mg/kg Rabeprazole sodium revealed no increased levels of gastrin and no ECL cell hyperplasia indicating that chronic stimulation of G cells and gastrin release is critical in the pathogenesis of hypergastrinemia and trophic gastric lesions. Reversibility of non-neoplastic changes was demonstrated in several studies in rats, mice and dogs. In mice diffuse neuroendocrine cell hyperplasia was fully restored and hyperplastic gastropathy was partially reversed after 13 or 26 weeks of recovery period.
Carcinogenicity	In a two-year carcinogenicity study in Fischer rats on a restricted feeding regime, ECL cell hyperplasia was observed but no gastric carcinoids were identified at doses up to 20 mg/kg/day (about 10 times the exposure on a body surface [mg/m^2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] dose). A second two-year carcinogenicity study was conducted in Sprague-Dawley rats on an ad libitum feeding regime given oral doses of Rabeprazole at 5, 15, 30 and 60 mg/kg/day for males and 5, 15, 30, 60 and 120 mg/kg/day for females (about 2-60 times the exposure on a body surface [mg/m2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] dose). Although ECL cell hyperplasia was

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	observed in both male and female rats and mice in the carcinogenicity studies, Rabeprazole produced dose-related gastric carcinoids only in female Sprague-Dawley rats at doses ≥5 mg/kg. Rabeprazole was not observed to induce tumours in any other tissue. In a two-year mouse carcinogenicity study, no drug-induced tumours were identified at doses up to 100 mg/kg/day (24 times exposure on a body surface [mg/m^2] basis for patients given the recommended 20 mg/day [12.3 mg/m^2] dose). In a 28-week mouse carcinogenicity study, a group of male and female p53 (+/-) C57BL/6 mice were administered Rabeprazole daily by oral gavage at levels of 0 (vehicle control), 20, 60 or 200 mg/kg/day. A positive control group received a dose level of 400 mg/kg/day of p-cresidine daily by oral gavage in the same manner. Treatment-related non-neoplastic changes were described in the report as mucosal hyperplasia of the glandular stomach. These changes were attributable to pharmacologic effects of Rabeprazole. There was no evidence of carcinogenic effect by Rabeprazole treatment in the stomach. A small number of neoplasms (malignant lymphoma) were observed in the study. The incidence of malignant lymphoma was 1/20 in middose males; 1/20 in each of low-, mid- and high-dose group females (or 5%). Four female mice treated with Rabeprazole died, three of them with malignant lymphoma. There was no dose response and the incidence of these neoplasms was not higher than expected based on the testing facility historical control data, or from data published by Storer, RD, et al. (that reported a historical incidence of malignant lymphoma in p53(+/-) C57BL/6 mice of 1.7-5.7% for males and 1.8-8% for females). The positive control group showed the expected tumour response, which is the development of mostly transitional cell carcinoma in the urinary bladder, thereby validating the study. The study was valid for detecting carcinogenic potential.
In vivo/In vitro Genotoxicity Studies	**Mutagenicity Studies Rabeprazole was not genotoxic** in the in vitro test for chromosome aberration in CHL/IU cells, the in vivo mouse micronucleus test, and the in vivo/ex vivo and in vitro unscheduled DNA synthesis assays in rat hepatocytes. The CHO/HGPRT Forward Gene Mutation Assay: There was no evidence of induced mutation by treatment with Rabeprazole at concentrations ranging from 10 to 40 mcg/mL in the activated test. A weak response for mutagenicity was observed at concentrations ranging from 90 to 110 mcg/mL in the absence of metabolic activation. However, this response was not reproducible. Treatment with either EMS or 3MC resulted in induction of HGPRT mutants. It was concluded that Rabeprazole was not mutagenic in HGPRT+ Chinese hamster ovary cells. Ames Tests : Positive and negative results were observed. Positive results were seen with the carboxylic acid metabolite (M6) of Rabeprazole which were attributable to contaminants originating from the reverse-phase chromatography column used for purifying M6. The L5178Y TK Mouse Lymphoma Assay: Rabeprazole was negative for inducing mutations in L5178Y TK+/- cells when testing in the absence of metabolic activation, but was weakly positive when tested at concentrations of 25 and 30 mcg/mL in the presence of metabolic activation.
Reproductive/Developmental Toxicity	Because the oral bioavailability of Rabeprazole sodium is low in rats and rabbits (less than 5%), Rabeprazole was administered intravenously in the reproduction studies to maximize systemic exposure. Male and female fertility (+2 generations), embryo-fetal development (EFD) and perinatal/postnatal (+2 generations) studies, and effects on luteinizing hormone (LH) and testosterone (T) were completed. In the fertility study (0, 1, 6, 30 mg/kg), no effects were observed on male or female fertility or on growth, development, or reproductive

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	performance of the F1 generation. At maternally toxic doses (25 and 50 mg/kg) in the rat EFD study, incomplete ossification of the parietal and/or occipital bones was observed. There were no other effects on viability, weight or morphology. At maternally toxic doses (30 mg/kg) in the rabbit EFD study, decreased fetal weight and delayed ossification of the proximal tibial epiphysis was observed. There were no other effects on fetal viability or morphology. Adequate absorption of Rabeprazole was demonstrated in the rabbit during the organogenesis period. In the perinatal/postnatal study in rats (0, 1, 6, 30 mg/kg), maternal toxicity was noted at 30 mg/kg, but this did not affect general reproductive performance or nursing of the dams. No effects on fetal development, parturition, lactation, postnatal growth and offspring development, or offspring reproductive performance were observed in this study. Lansoprazole-induced Leydig cell tumours in the rat testes are related to an imbalance of LH regulation (Atkinson-1990). Rabeprazole does not cause Leydig cell tumours or perturbations of the LH/T axis.
Highly Sensitizing Potential	Rabeprazole can cause a severe allergic reaction. Symptoms can include: • Rash • Swelling of your face • Throat tightness • Trouble breathing

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any an adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	**Clinical therapeutics:** ○ **To treat gastroesophageal reflux disease (GERD):** ▪ Children 1 to 11 years of age and weighing 15 kilograms (kg) or more-10 milligrams (mg) once a day. ▪ Children 1 to 11 years of age and weighing less than 15 kg-5 mg once a day. ○ **To treat duodenal ulcers:** ▪ Adults-20 milligrams (mg) once a day after the morning meal for up to 4 weeks. ○ **To treat duodenal ulcers with *H. pylori* infection:** ▪ Adults-20 milligrams (mg) taken with a meal 2 times a day for 7 days. ○ **To treat gastroesophageal reflux disease (GERD):** ▪ Adults-20 milligrams (mg) once a day for up to 4 weeks. ▪ Children 12 years of age and older-20 mg once a day for up to 8 weeks. ○ **To prevent gastroesophageal reflux disease (GERD):** ▪ Adults-20 milligrams (mg) once a day. ○ **To treat Zollinger-Ellison syndrome:** ▪ Adults-At first, 60 milligrams (mg) once a day. **Adverse effects:** Worldwide, over 3094 patients have been treated with Rabeprazole sodium in Phase II-III clinical trials involving various dosages and durations of treatment. In general, Rabeprazole treatment has been well tolerated in both short-term and long-term trials.

NOAEL/LOAEL	The NOAEL of the 90 day study in dogs was 3 mg/kg.

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APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2	For extrapolation from Dog to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	Short duration study in non-rodent (90 days).
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	The NOAEL of the 90 day study in dogs was 3 mg/kg.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{3 (NOAEL) x 50}}{\text{2 x 10 x 10 x 1 x 5}}$ = 0.15 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Rabeprazole
- https://www.fda.gov/media/71693/download
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Rabeprazole_TAB_Monograph.pdf
- https://www.healthline.com/health/rabeprazole-oral-tablet#other-warnings