PERMITTED DAILY EXPOSURE FOR ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

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 Esomeprazole Magnesium Trihydrate 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:

Esomeprazole is a medication which reduces stomach acid. It is used to treat gastroesophageal reflux disease, peptic ulcer disease, and Zollinger–Ellison syndrome. Effectiveness is similar to other proton pump inhibitors (PPIs).

3. IDENTITY OF THE ACTIVE SUBSTANCE:

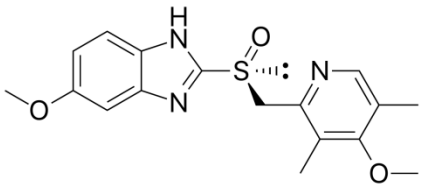
IUPAC name: (S)-(−)-5-Methoxy-2-[(4-methoxy-3, 5-dimethylpyridin-2-yl) methylsulfinyl]-3H-benzoimidazole

Chemical Abstract Services (CAS) Registry Number: 119141-88-7

Molecular Weight: 345.417 g/mol g·mol^{-1}

Chemical Formula: $C_{17}H_{19}N_3O_3S$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

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SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Esomeprazole accumulates in the acidic environment of the parietal cells after absorption, where it is converted into the active form. This active sulphenamide specifically binds the H+, K+- ATPase (proton pump), to block the final step in acid production, thus reducing gastric acidity. Esomeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion. In healthy male subjects (n=12), repeated administration with 20 mg esomeprazole magnesium once daily for 5 days, decreased mean peak acid output after pentagastrin stimulation by 90% when measured 6 to 7 hours after dosing. The effect of antisecretory therapy can be predicted from the duration of suppression of intragastric acidity to above pH 4.0 achieved by each drug regimen, and the length of treatment. The antisecretory activity of esomeprazole magnesium was studied in patients with nonerosive reflux disease. Esomeprazole magnesium 20 and 40 mg tablets were administered over 5 days and the proportion of time when intragastric pH was > 4 over a 24 hour period was assessed on Day 5.
Pharmacokinetics data	Single 20 to 40 mg oral doses generally give rise to peak plasma esomeprazole concentrations of 0.5-1.0 mg/l within 1–4 hours, but after several days of once-daily administration, these levels may increase by about 50%. A 30-minute intravenous infusion of a similar dose usually produces peak plasma levels on the order of 1–3 mg/l. The drug is rapidly cleared from the body, largely by urinary excretion of pharmacologically inactive metabolites such as 5-hydroxymethylesomeprazole and 5-carboxyesomeprazole. Esomeprazole and its metabolites are analytically indistinguishable from omeprazole and the corresponding omeprazole metabolites unless chiral techniques are employed.
Acute Toxicity	**Study 1:** In an acute, single-dose toxicity study (Study # B06132) in SD rats (5/sex/dose, 7 weeks old), both EST (1000 and 2000 mg/kg) and EMT (500, 1000, and 2000 mg/kg) produced treatment-related deaths. Treatment with EMT produced more central nervous system (CNS) related clinical signs (convulsions, inanimation, lacrimation, salivation) and death, as compared to EST. The maximum tolerated dose (MTD) of EST in rats was ≤ 1000 mg/kg in males and 2000 mg/kg in females. In contrast the MTD of EMT was ≤ 1000 mg/kg in males and 500 mg/kg in females. In a dose escalation study (Study # B06134), beagle dogs (2/sex, 6 months old) were administered a single oral dose of either EST or EMT (10, 25, 50, 250, 1000 mg/kg) with a 7-day washout period between dosing intervals. Overall, EST showed a toxicity profile similar to EMT. One high dose EMT female died within 1 day of dosing. There was a dose-dependent increase in CNS-related clinical signs (salivation, vocalization, head nodding, tonic extension of limbs and convulsions) at ≥ 25 mg/kg EST or EMT in both sexes, within the first half hour and lasted up to 2 days post-dose in some animals. GI-related clinical signs included dyspepsia, nausea, vomiting and diarrhea in both treatment groups. There were no treatment-related changes in body weight or food consumption. Based on these data, the No Observed Adverse Effect Level (NOAEL) dose for EST in dogs was 10 mg/kg. The MTD for EST in males and females was ≥ 1000 mg/kg.

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SUMMARY OF HAZARD IDENTIFICATION:

Study 2:

Species	Sex	Route	LD50
Rat	M	p.o.	930
	P	p.o.	480
Rat	M	i.v.	290
	P	i.v.	290

The single dose toxicity of esomeprazole was studied in Wistar rats following oral and i.v. administration and compared to that of omeprazole. The effects of esomeprazole, administered either intravenously or orally, were similar to those previously reported for omeprazole. A small but clear difference in response between the sexes was seen. The main signs of acute toxicity were reduced motor activity, coupled with changes in respiratory frequency and abdominal respiration. Intermittent clonic convulsions, sometimes associated with dyspnea, increased salivation, cyanosis, tremor, ataxia and/or very reduced motor activity were also seen. Death occurred within 23 hours of oral treatment or 2 hours of i.v. administration.

Repeated Dose Toxicity (Chronic Toxicity)

Study 1: In a 13-week repeat-dose oral toxicity study (Study # B06133), SD rats (10/sex/dose, 6 weeks old) received 14, 69, and 280 mg/kg/day EST, 280 mg/kg EMT, or vehicle (0.05% Carboxymethylcellulose). Except for the dosing-related death of one high dose female on Day 46, there were no other unscheduled deaths during the dosing period. Salivation was observed consistently at 69 and 280 mg/kg EST and 280 mg/kg EMT from Day 3 onwards, throughout the dosing period. Females at all doses of EST showed a decreasing trend in body weight gain, with the greatest decrease in the high dose females (~30%, similar to 280 mg/kg/day EMT-treated females). Males treated with EST or EMT at the highest dose showed a decrease in body weight gain of ≤ 16.6%, as compared to controls, during the dosing period. There was a decrease in hemoglobin, hematocrit, mean corpuscular volume, mean cell hemoglobin (MHC), MHC concentration (MCHC), and eosinophil concentration in the high dose treatment groups (280 mg/kg/day EST or EMT) in males and females, as compared to controls. There were increases in absolute and relative (relative to body weight) liver and kidney weight in the high dose groups (280 mg/kg) for both EST and EMT, as compared to vehicle. The increase in kidney weight correlated with Histopathological findings of tubular regeneration in both males and females treated with 69 and 280 mg/kg/day EST and 280 mg/kg/day EMT. Histopathological analysis also revealed lesions and areas of degeneration in the stomach (eosinophilic granular degeneration) in the same treatment groups in both sexes. No other significant, treatment-related changes in histopathology were noted. Both EST and EMT showed dose-dependent increases in systemic exposure, with potential drug accumulation after repeated administration, which correlated with the consistent observation of clinical signs after Day 3 of the dosing period. The Cmax was reached at 0.17 to 0.61 h post dose and plasma t1/2 was estimated to be between 2 and 19 h. Overall, females had higher systemic exposure to drug than males. Based on these data, the NOAEL dose of EST for males and females was determined to be 14 mg/kg.

Study 2:
The repeat-dose toxicity of esomeprazole was studied in rats (Wistar and

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SUMMARY OF HAZARD IDENTIFICATION:	
	Sprague-Dawley) and dogs after oral administration. Rats received oral doses of 14-280 mg/kg, and dogs 0.66-28 mg/kg, for up to 3 months. Esomeprazole has a low systemic toxicity. Some slight haematological changes indicating a mild microcytic, hypochromic anaemia (possibly due to aniron deficiency) were observed in adult rats, following repeat-dose ora treatment with high doses of esomeprazole or omeprazole. Similar slight changes were seen in pregnant rabbits, but no such changes were noted in esomeprazole-treated dogs. In both rats and dogs, histopathological changes in the stomach at the intermediate and high dose levels (rats: 69 and 280 mg/kg; dogs: 5.5 and 28 mg/kg) consisting of dose-dependent chief cell atrophy, mucosal hyperplasia, and/or focal necrosis of gastric glands, were accompanied by a dose-dependent increase in stomach weight and serum gastrin levels. These changes were expected and consistent with previous observations following treatment with high doses of omeprazole. These effects are the results of gastrin stimulation and/or inhibition of gastric acid secretion.
Carcinogenicity	**Study 1:** Long-term toxicity studies of omeprazole, revealed the gastric mucosa as the target organ. The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In the rat carcinogenicity study (24 months), ECL-cell carcinoids were found in some animals treated with 14-140 mg/kg/day for their normal life span. ECL-cell carcinoids were seen in a background of ECL-cell hyperplasia. No ECL-cell carcinoids were identified in the carcinogenicity study in mice or in long-term (up to 7 years) general toxicity studies in dogs. A vast number of studies have revealed that pronounced and sustained hypergastrinemia is the mechanism behind the development of the gastric ECL-cell carcinoids in the rat. Such ECL carcinoids have been seen in rats after life-long treatment with other inhibitors of acid secretion such as H2-receptor blockers and other proton pump inhibitors. Partial fundectomy in rats results in hypergastrinemia and gastric ECL-cell carcinoids in the remaining part of the fundic mucosa, towards the end of the rats' life span. **Treatment with esomeprazole magnesium for up to 1 year in more than 800 patients has not resulted in any significant pathological changes in the gastric oxyntic endocrine cells.** Short-term treatment and long-term treatment with the racemate, omeprazole, capsules in a limited number of patients for up to 11 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells. During treatment with all antisecretory drugs serum gastrin increases in response to the decreased acid secretion. The effect of esomeprazole magnesium on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months (daily doses of either 20 or 40 mg). The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau (approximately 100 pg/mL) within two to three months of therapy and returned to baseline levels (approximately 30-40 pg/mL) within four weeks after discontinuation of therapy. **Study 2:** An 18-month oral study was conducted in mice at doses of 14, 44 and 140 mg/kg/day of omeprazole. No evidence of carcinogenic potential was seen. A 24-month oral study was conducted in rats at doses of 14, 44 and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumour-like proliferations in the stomach. Histology showed a continuum from diffuse

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SUMMARY OF HAZARD IDENTIFICATION:	
	ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumour-like proliferations, some extending into the sub-mucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in Sandoz Esomeprazole Product Monograph 46 female rats. No metastases were identified in any of the animals. Carcinoids have not been observed after long-term administration of omeprazole to mice and dogs.
In vivo/In vitro Genotoxicity Studies	Esomeprazole was not mutagenic in an in vitro Ames Salmonella test, but was clastogenic in an in vitro chromosome aberration test in peripheral human lymphocytes. When compared head to head in another study in peripheral human lymphocytes, esomeprazole, omeprazole, the R-enantiomer of omeprazole and lansoprazole induced the same type and degree of chromosome aberrations. Esomeprazole did not show any evidence of mutagenic potential in vivo in a mouse micronucleus test or in a chromosome aberration test in rat bone marrow in spite of extensive exposure.
Reproductive/Developmental Toxicity	Slight maternal toxicity was noted in pregnant rats treated orally with esomeprazole or omeprazole at doses of up to 280 mg/kg/day, but no adverse effects could be detected on embryo-foetal survival or development. The systemic exposure to esomeprazole in these animals was substantially higher than that seen in the clinical situation, indicating an adequate margin of safety. Neither did treatment of pregnant rabbits with esomeprazole or omeprazole indicate any potential for disturbance of embryo-foetal development. However, severe and dose-related maternal toxicity was noted at relatively low doses and exposure of esomeprazole/omeprazole, resulting in some minor litter effects (a slight reduction in fetal weight and a small increase in the incidence of minor skeletal defects at doses of 26 and 86 mg/kg/day). Although exposure to esomeprazole was relatively low in many of the does, the highest dose level used could not be increased due to this maternal toxicity
Highly Sensitizing Potential	No skin sensitivity observed.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Gastric ECL-Cell Carcinoids Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. In one series of experiments, the antrum of rats was surgically excluded from the rest of the stomach. The removal of acid from the antrum in this way led to pronounced hypergastrinemia and, secondary to this, gastric ECL-cell proliferation. Antrectomy, which removes the source of gastrin, led to hypogastrinemia and a decrease in gastric ECL-cell density. These experiments indicated that gastrin has a direct trophic effect on gastric ECL-cells. In another series of experiments, high doses of omeprazole and a histamine H2-receptor blocker caused hypergastrinemia and increased ECL-cell density. In antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that (i) inhibition of gastric acid secretion by large doses of omeprazole or a histamine H2-receptor blocker evokes a natural feedback response leading to hypergastrinemia, (ii) longstanding hypergastrinemia leads to gastric ECLcell proliferation, and (iii) there is no direct trophic effect of omeprazole on gastric ECL-cells. An additional

	long-term (24 months) toxicity study of omeprazole in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumours and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8- 140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found, and the ECL-cell hyperplasia seen after 12 months recovered to normal during the next 12 months of no treatment. No carcinoids were found in the mice carcinogenicity study over 18 months, in a 6-month carcinogenicity bioassay conducted with omeprazole in p53± heterozygous and C57BL/6 (background strain) mice at dose levels of up to 830 mg/kg/day, or in dogs following administration of 0.17 mg/kg/day omeprazole for 7 years. Treatment with esomeprazole magnesium for up to 1 year in more than 800 patients resulted in moderate increases in serum gastrin levels. However, no significant pathological changes in the gastric oxyntic endocrine cells were observed.
Clinical therapeutic and adverse effects	Adults dose for Esomeprazole: 20 to 40 mg once a day for 2 to 8 weeks. Long-term use of PPI's (Proton Pump Inhibitor) in patients treated for Helicobacter pylori has been shown to dramatically increase the risk of gastric cancer.

NOAEL/LOAEL	14 mg/kg is the NOAEL dose.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	5	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	5	3 months study available in rodent.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed, although patients treated for Helicobacter pylori has been shown to dramatically increase the risk of gastric cancer.
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{14 (NOAEL) x 50}}{\text{5 x 10 x 5 x 1 x 5}}$ = 0.56 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Esomeprazole
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202342Orig1s000PharmR.pdf.
- https://www.sandoz.ca/sites/www.sandoz.ca/files/9530-Sandoz%20Esomeprazole%20Consumer%20Information.
- https://pubchem.ncbi.nlm.nih.gov/compound/Esomeprazole#section=DrugBank-Interactions.