PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE 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 Pantoprazole 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:

Pantoprazole is a medication used for the treatment of stomach ulcers, short-term treatment of erosive esophagitis due to gastroesophageal reflux disease (GERD), maintenance of healing of erosive esophagitis, and pathological hypersecretory conditions including Zollinger–Ellison syndrome. It may also be used along with other medications to eliminate Helicobacter pylori. Effectiveness is similar to other proton pump inhibitors (PPIs). It is available by mouth and by injection into a vein.

Common side effects include headaches, diarrhea, vomiting, abdominal pain, and joint pain. More serious side effects may include severe allergic reactions, a type of chronic inflammation known as atrophic gastritis , Clostridium difficile colitis, low magnesium, and vitamin B12 deficiency. Use in pregnancy appears to be safe. Pantoprazole is a proton pump inhibitor that decreases gastric acid secretion. It works by inactivating (H+/K+)-ATPase function in the stomach.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Physical description: White to off-white powder

Solubilities in common solvents: Pantoprazole sodium sesquihydrate is freely soluble in ethanol and water, and practically insoluble in hexane.

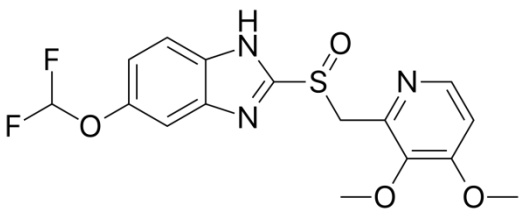
IUPAC name: (RS)-6-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzo[d]imidazole

Chemical Abstract Services (CAS) Registry Number: 102625-70-7

Molecular Weight: 383.371 g/mol g·mol−1

Chemical Formula: $C_{16}H_{15}F_2N_3O_4S$

Molecular Structure:



PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Mechanism of Action Pantoprazole sodium is a specific inhibitor of the gastric H+ , K+ -ATPase enzyme (the proton pump) that is responsible for acid secretion by the parietal cells of the stomach. Pantoprazole sodium is a substituted benzimidazole that accumulates in the acidic environment of the parietal cells after absorption. Pantoprazole sodium is then converted into the active form, a cyclic sulphenamide, which binds to the H+ , K+ -ATPase, thus inhibiting both the basal and stimulated gastric acid secretion. Pantoprazole sodium exerts its effect in an acidic environment (pH < 3), and it is mostly inactive at higher pH. Its pharmacological and therapeutic effect is achieved in the acid-secretory parietal cells. In clinical studies investigating intravenous (IV) and oral administration, pantoprazole sodium inhibited pentagastrin-stimulated gastric acid secretion. With a daily oral dose of 40 mg, inhibition was 51% on Day 1 and 85% on Day 7. Basal 24-hour acidity was reduced by 37% and 98% on Days 1 and 7, respectively. In long-term international studies involving over 800 patients, a 2 to 3 fold mean increase from the pre-treatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials. Pharmacodynamics Pantoprazole is a proton pump inhibitor. It inhibits H+ ,K+ -ATPase, the enzyme responsible for gastric acid secretion in the parietal cells of the stomach, in a dose-dependent manner. The drug is a substituted benzimidazole that accumulates in the acid canaliculi of parietal cells after absorption. There, pantoprazole is converted into the active form, a cyclic sulfenamide that binds selectively to the proton translocating region of the H+ ,K+ -ATPase. Pantoprazole's selectivity is due to the fact that it only exerts its maximal effect in a strongly acidic environment (pH<3). Pantoprazole remains mostly inactive at higher pH values. As pantoprazole action is distal to the receptor levels, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).
Pharmacokinetics data	Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:

Absorption: Pantoprazole is completely and rapidly absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77 %. On average, at about 2.0 h - 2.5 h post administration (tmax) of a single 20 mg oral dose, the maximum serum concentrations (Cmax) of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. Concomitant intake of food had no influence on bioavailability (AUC or Cmax), but increased the variability of the lag-time (tlag).

Distribution: Volume of distribution is about 0.15 l/kg and serum protein binding is about 98%.

Metabolism and excretion: Clearance is about 0.1 l/h/kg, and terminal half-life (t1/2) about 1 h. There were a few cases of subjects with delayed elimination. Due to the specific binding of pantoprazole to the proton pumps within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion). Pantoprazole is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest is excreted with the faeces. The main metabolite in both serum and urine is desmethylpantoprazole, which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Acute Toxicity

In acute toxicity studies in mice the mean lethal dose (LD50) values for pantoprazole were found to be around 390 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration. In the rat the corresponding values were around 250 mg/kg for i.v. administration and > 1000 mg/kg for oral administration. Acute toxicity studies were conducted on B8810-044, the major degradation product of pantoprazole. The approximate LD50 values for mice (119-167 mg/kg) and rats (73-82 mg/kg) were lower than those for pantoprazole itself, after intravenous injection, but the toxic symptoms were similar to those noted for the drug. A 4-week repeat dose study was also conducted using this degradation product using the intravenous route in rats. Rats received 5 and 25 mg of B8810- 044/kg, while a comparison group received 25 mg/kg of pantoprazole. Muscle twitches were observed immediately after injection in rats receiving 25 mg/kg of the degradation product, but not in the pantoprazole-treated animals. Otherwise the compounds were comparable.

Species	Sex	Route	Ca, ld50* (mg/kg)
Mouse	M	p.o.	>1000
	F	p.o.	747
Mouse	M	i.v.	399
	F	i.v.	395

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:

Rat	M	p.o.	1343
	F	p.o.	1037
Rat	M	i.v.	330
	F	i.v.	343
Dog	M/F	p.o.	300-1000
	M/F	i.v.	150-300

The symptoms seen after lethal oral or i.v. doses were similar in rats and mice: the animals displayed ataxia, reduced activity, hypothermia and prostration. Surviving animals recovered uneventfully. Salivation, tremor, lethargy, prostration and coma were seen in dogs at lethal oral doses, with death occurring on the following day. Ataxia, tremor and a prone position were noted at sublethal oral and i.v. doses, but the survivors recovered quickly and appeared fully normal after the 2-week observation period.

Repeated Dose Toxicity (Chronic Toxicity)

Daily oral doses of pantoprazole in the 1- and 6-month SD rat repeated-dose studies were 1, 5, 20, and 500 mg/kg and 0.8, 4, 16 and 320 mg/kg, respectively; doses for the 1 month rat pantoprazole i.v. study were 1, 5, and 30 mg/kg. A 12-month toxicity study in SD rats was conducted using daily oral doses of 5, 50, and 300 mg/kg. Daily oral doses in the 1- and 6 month (beagle) dog studies were 7.5, 15, 30, and 100 mg/kg and 5, 15, 30, and 60 mg/kg respectively. In the 12-month oral study in dogs, 2.5, 15, and 60 mg/kg were administered daily. Hypergastrinemia was dose-related and was observed at all doses investigated in the studies mentioned above, but was reversible upon cessation of treatment. Drug-related effects on the stomach included increased stomach weights and morphologic changes of the mucosal. After intravenous administration, the only morphologic change seen in the rat stomach was an increased incidence of eosinophilic chief cells in the glandular stomach. In the 6-month rat study, increased stomach weight and some cellular changes were detected at all doses. In the 1-month rat study, gastric changes were detected at 5 mg/kg but not at 1 mg/kg. In dogs, increased stomach weight was observed at all doses studied. There were no gastric cellular changes detected at oral doses of 7.5 or 5 mg/kg in the 1- and 6-month dog studies, respectively. In both species, most gastric effects were reversible after a 4- or 8-week recovery period. Hypergastrinemia and gastric changes were considered to be the consequence of the pharmacological action of the compound, namely prolonged and profound inhibition of acid secretion. Increased liver weight in the rat experiments was considered to be a consequence of the induction of hepatic drug metabolizing systems and was found to be associated with centrilobular hepatocellular hypertrophy at 320 mg/kg in the 6-month study and at 50 and 300 mg/kg after 12 months of treatment. Increased liver weights were also detected at a dose of 16 mg/kg in male rats in the 6-month study and at 500 mg/kg, but not 20 mg/kg, in the 1-month study. Increased liver weight was noted in male dogs of all dose groups in the 1-month study, though only at 100 mg/kg in females on the same study. Both

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:	
	males and females had increased liver weights after 6 months administration of 30 or 60 mg/kg, but not as 15 mg/kg. In the 12-month study, liver weights were increased only in the female dogs dosed with 60 mg/kg. There were no hepatic lesions that correlated with increased liver weight in the dog studies. In dogs, the increase in liver weight was attributed to an activation of hepatic drug metabolizing systems as mentioned for rats. Thyroid activation in animal experiments is due to the rapid metabolization of thyroid hormones in the liver and has been described in a similar form for other drugs. Thyroid weights were increased in both sexes at 500 mg/kg in the 1-month rat study and at 320 mg/kg in the rat 6-month study. Thyroid follicular cell hypertrophy was noted in females at these doses, in rats treated with 50 and 300 mg/kg in the 12 month study and also in a few females at 16 mg/kg in the 6 month study. There were no thyroid effects in rats at or below an oral dose of 5 mg/kg even after 1 year. In the dog, no effects were seen on the thyroid after 4 weeks. Only slight, but not dose-dependent, increases in thyroid weights were seen after 6 months, but no changes were observed histologically. In the 12 month study, the relative thyroid weights in the 60 mg/kg group were only slightly higher than those of the control dogs, and changes were detected histologically in only a few animals under 15 and 60 mg/kg. In both species, changes were reversible. Increased serum cholesterol values were noted in all groups in the 6- and 12 month dog studies and in all groups in the 12 month rat study. The increases were slight and were reversible after cessation of treatment. In dog studies, oral doses of pantoprazole of 15 mg/kg or above caused a transient pulmonary edema in a proportion of naive dogs during the first week of drug administration. Pulmonary edema caused death in a few dogs after repeated oral doses of 15 mg/kg or above. There is strong evidence that the pulmonary toxicity is due to a thiol metabolite which does not occur in man. No evidence of pulmonary edema was detected in dogs at an oral dose of 7.5 mg/kg nor at 60 mg/kg when administered daily for 6 or 12 months after a 1 week dose escalation phase.
Carcinogenicity	Carcinogenicity Three carcinogenicity studies have been conducted: • A 24 month oral study was conducted at doses of 0.5, 5, 50 and 200 mg/kg/day in SD rat. • A 24 month oral study was conducted at doses of 5, 15 and 50 mg/kg/day in Fischer-344 rats. • A 24 month oral study was conducted at doses of 5, 25 and 150 mg/kg/day in B6C3F1 mouse. Pantoprazole, dissolved in distilled water, was administered once a day by oral gavage to groups of 50 male and 50 female B6C3F1 mice at doses of 5, 25, or 150 mg/kg. An identical control group was dosed with distilled water (pH 10), while a second identical control group received no treatment at all. In the first rat study, pantoprazole was administered once a day by oral gavage to groups of 70 male and 70 female SD rats at doses of 0.5, 5, 50, and 200 mg/kg. A control group of 70 males and 70 females received the vehicle. In the second rat study, pantoprazole was administered once a day by oral gavage to groups of 50 male and 50 female Fischer-344 rats at doses of 5, 15, and 50 mg/kg. A control group

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:	
	of 50 males and 50 females received the vehicle, while another group remained untreated. In the first 2 year carcinogenicity study in rats, which corresponds to a lifetime treatment for rats, neuroendocrine neoplasms were found in the stomach at doses of 50 mg/kg/day and above in males and at 0.5 mg/kg/day and above in females. Tumor formation occurred late in the life of the animals (only after 17 months treatment), whereas no tumors were found in rats treated with an even higher dose for 1 year. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated, and it is considered to be due to high levels of serum gastrin observed in the rat during chronic treatment. In the second rat carcinogenicity study, neuroendocrine cell tumors in the stomach were found in all treated female groups and in the male 15 and 50 mg/kg groups. ECL-cell neoplasms were not observed in either the carcinogenicity study in the mouse (24 months) or in the chronic studies in the dog. In clinical studies, where pantoprazole was administered at doses up to 80 mg, ECL-cell density remained almost unchanged. Microscopy of the rat (first carcinogenicity study) and mouse tissues gave evidence for an increase in liver tumors. In the rat experiment, the incidence of benign liver tumors in the 50 and 200 mg/kg groups and the incidence of hepatocellular carcinoma was increased in the males and females of the 200 mg/kg group. There was a slightly higher incidence of hepatocellular adenomas and carcinomas in the female mice of the 150 mg/kg group than in either of the 2 control groups. Other changes in the liver morphology were present as well. Centrilobular hepatocellular hypertrophy increased in incidence and severity with increasing dose, and hepatocellular necrosis was increased in the highest dose in the rat and mouse studies. Hepatocellular tumors are common in mice, and the incidence found for the female 150 mg/kg group was within historical control ranges for this strain. The liver tumor incidences in rats treated with 50 mg/kg and in the male rats treated with 200 mg/kg were also within historical control incidences for the rat. These tumors occurred late in the life of the animals and were primarily benign. The nongenotoxic mechanism of rodent liver tumor formation after prolonged treatment with pantoprazole is associated with enzyme induction leading to hepatomegaly and centrilobular hypertrophy and is characterized by tumor induction in low incidences at high doses only. As pantoprazole acts in a similar fashion to phenobarbital, causing reversible centrilobular hepatocellular hypertrophy and enzyme induction in short-term studies, it is probable that the mechanism of action for induction of the liver tumors seen in longterm rodent studies is also the same. Hepatocellular tumors at high doses in rodents are not indicative of human carcinogenic risk. A slight increase in neoplastic changes of the thyroid was observed in rats receiving pantoprazole at 200 mg/kg/day. The incidences of these tumors were within the historical control ranges for this rat strain. No thyroid neoplasms were observed in the 12-month study. The no-effect dose for both male and female rats is 50 mg/kg, which is 100 times the most commonly used human dose (i.e. 40 mg). The effect of pantoprazole on the thyroid is secondary to the effects on liver enzyme induction, which lead to enhanced metabolism of thyroid hormones in the liver. As a consequence, increased TSH is produced, which has a trophic effect on the thyroid gland. Clinical studies have demonstrated that neither liver

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:	
	enzyme induction nor changes in thyroid hormonal parameters occur in man after therapeutic doses of pantoprazole. Tumors induced in rats and mice by pantoprazole were the result of nongenotoxic mechanisms which are not relevant to humans. Tumors were induced in rodents at dosages that provide higher exposure than with human therapeutic use. Based on kinetic data, the exposure to pantoprazole in rats receiving 200 mg/kg was 22.5 times higher than that found in humans receiving 40 mg oral doses. In mice receiving 150 mg/kg, exposure to pantoprazole was 2.5 times higher than that in humans.
In vivo/In vitro Genotoxicity Studies	In the 2-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the 2-year rodent studies an increased number of liver tumors was observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one 2-year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected. **Pantoprazole was studied in several mutagenicity studies:** Pantoprazole was found negative in the Ames test, an in vivo chromosome aberration assay in rat bone marrow, a mouse lymphoma test, two gene mutation tests in Chinese hamster ovary cells in vitro, and two micronucleus tests in mice in vivo. Pantoprazole was found positive in three of four chromosome aberration assays in human lymphocytes in vitro. The in vitro tests were conducted both in the presence and absence of metabolic activation. The potential of pantoprazole to induce DNA repair synthesis was tested negative in an in vitro assay using rat hepatocytes. In addition, a rat liver DNA covalent binding assay showed no biologically relevant binding of pantoprazole to DNA. In addition, two in vitro cell transformation assays using different cell types were performed to aid in the interpretation of the rodent carcinogenicity studies; in neither test did pantoprazole enhance the morphologic transformation of the cell types used. A bacterial mutation assay conducted with the degradation product B8810-044, gave no indication of a mutagenic potential.
Reproductive/Developmental Toxicity	**In animal studies (rats) 5 mg/kg was the observed NOAEL** (No Observed Adverse Effect Level) for embryotoxicity. Investigations revealed no evidence of impaired fertility or teratogenic effects. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

SUMMARY OF HAZARD IDENTIFICATION:	
	pantoprazole in the foetus is increased shortly before birth. Pantoprazole was not teratogenic to rats or rabbits at doses up to 450 and 40 mg/kg/day (gavage), 20 and 15 mg/kg/day (i.v. injection), respectively. Treatment of male rats with pantoprazole up to 500 mg/kg p.o. for 127 days did not affect fertility. Treatment of pregnant rats induced dose-dependent fetotoxic effects: increased pre- and postnatal deaths (450 mg/kg/day), reduced fetal weight and delayed skeletal ossification (150 mg/kg/day), and reduced pup weight (15 mg/kg/day). These results may be explained by maternal toxicity of pantoprazole at high dose and/or placental transfer of pantoprazole. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the fetus is increased shortly before birth regardless of the route of administration. In humans, there are no adequate or well-controlled studies with the use of pantoprazole during pregnancy.
Highly Sensitizing Potential	Though it's rare, pantoprazole can cause an allergic reaction. Symptoms could include rash, swelling, or breathing problems.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	*Usual Adult Dose for Erosive Esophagitis:* 40 mg orally once a day for up to 8 weeks *Usual Adult Dose for Gastroesophageal Reflux Disease:* Oral: 40 mg orally once a day, for short-term administration (up to 8 weeks). *Usual Adult Dose for Duodenal Ulcer:* 40 mg orally once a day, dose was increased every 12 weeks by 40 mg increments to a maximum of 120 mg per day, for 28 weeks. *Usual Adult Dose for Gastric Ulcer:* 40 mg orally once a day. Usual Adult Dose for Helicobacter pylori Infection: 40 mg orally twice daily for 7 days *Usual Adult Dose for Zollinger-Ellison Syndrome:* Oral: 40 mg twice daily, to a maximum of 240 mg per day. *Usual Adult Dose for Stress Ulcer Prophylaxis:* 80 mg twice daily, as a bolus infusion over a period of 15 minutes, to a maximum daily dose of 240 mg, divided into three equal doses. *Usual Adult Dose for Peptic Ulcer:* 80 mg twice daily, as a bolus infusion over a period of 15 minutes, to a maximum daily dose of 240 mg, divided into three equal doses. **Adverse effects:** • **Long-term use of pantoprazole can lead to an increased risk of certain side effects and complications. These include:**

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

	1. Increased risk of bone fracture in people taking higher, multiple daily doses for more than one year. 2. Vitamin B-12 deficiency, which can lead to serious nerve damage and deteriorating brain functions. This has been seen in some people taking pantoprazole for longer than three years. 3. Chronic inflammation of the stomach's lining (atrophic gastritis) when taking pantoprazole long term. People with *H. pylori* are particularly at risk. 4. Low blood magnesium (hypomagnesemia), this has been seen in some people taking pantoprazole for as few as three months. More often, it occurs after a year or more of treatment. • **Severe diarrhea warning:** Severe diarrhea caused by *Clostridium difficile* bacteria can occur in some people treated with pantoprazole, especially hospitalized people. • **Cutaneous lupus erythematosus and systemic lupus erythematosus warning:** Pantoprazole can cause cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE). CLE and SLE are autoimmune diseases. Symptoms of CLE can range from a rash on the skin and nose, to a raised, scaly, red or purple rash on certain parts of the body. Symptoms of SLE can include fever, tiredness, weight loss, blood clots, heartburn, and stomach pain. If you have any of these symptoms, call your doctor. • **Fundic gland polyps warning:** Long-term use (especially over one year) of pantoprazole can cause fundic gland polyps. These polyps are growths on the lining of your stomach that can become cancerous. To help prevent these polyps, you should use this drug for as short a time as possible.

NOAEL/LOAEL	In animal studies (rats) 5 mg/kg was the observed NOAEL (No Observed Adverse Effect Level) for Embryo toxicity.

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)	10	Short duration of 21 days study in rodent (gestation period)
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	In animal studies (rats) 5 mg/kg was the observed NOAEL (No Observed Adverse Effect Level) for Embryo toxicity.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

CALCULATION	
PDE Calculation	NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg) F1 x F2 x F3 x F4 x F5 = 5 (NOAEL) x 50 5 x 10 x 10 x 1 x 5 = 0.1 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Pantoprazole
- http://www.shijiebiaopin.net/upload/product/201432019460527.pdf
- http://www.auropharma.ca/products/monograph/Pantoprazole%20for%20Injection%20PM.pdf