PANTOPRAZOLE SODIUM SESQUIHYDRATE (INJECTION):
DETERMINATION OF PERMISSIBLE DAILY EXPOSURE (PDE) VALUE
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# 1. BASIC INFORMATION

| Toxicological Profile, Hazards Identification, Risk Assessment and Permissible Daily Exposure (PDE) Monograph of Pantoprazole Sodium |
|---|---|
| **PDE Value** | 2.325 mg/day |
| **Chemical name (IUPAC Name)** | Sodium;5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]benzimidazol-1-ide |
| **Drug product** | Pantoprazole Sodium (Injection) |
## 2. HAZARDS IDENTIFIED

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</thead>
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<tr>
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</tr>
</tbody>
</table>
PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE)

| PDE value | 2.325 mg/day |

HAZARD IDENTIFICATION

Pharmacodynamics data

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Acute toxicity

Acute oral and intravenous toxicity of pantoprazole sodium was determined in rats and mice. The observed clinical signs in rats and mice were similar and the animals displayed ataxia, reduced activity, hypothermia and prostration.

Repeted dose toxicity

Repeated dose toxicity studies were conducted in rats and dogs up to one year. In rats, treatment related changes in stomach, liver and thyroid was observed. In case of dogs, hypergastrenemia and changes in stomach was noticed.

Carcinogenicity

A total of three carcinogenicity studies were conducted, two with rats and one with mice. Neuroendocrine neoplasm of stomach in rats and hepatocellular carcinoma in mice was observed.

Genotoxicity studies

Pantoprazole was positive in the in vitro human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the in vitro Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the in vivo rat liver DNA covalent binding assay. Pantoprazole was negative in the in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the in vitro AS52/GPT mammalian cell-forward gene mutation assay, the in vitro thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the in vivo rat bone marrow cell chromosomal aberration assay.

Reproductive/Developmental toxicity

Pantoprazole sodium did not affect reproductive and development of fetus in rats and rabbits up to 450 and 40 mg/kg/day (gavage), respectively.

IDENTIFICATION OF CRITICAL EFFECTS
## Permitted Daily Exposure for Pantoprazole Sodium

| Sensitive indicator of an adverse effect seen in non-clinical toxicity data | In the repeated dose toxicity studies, treatment related changes in stomach, liver and thyroid was observed in rats and dogs. Pantoprazole sodium caused neuroendocrine neoplasm in stomach and hepatocellular carcinoma in rats and mice, respectively. |
| Clinical therapeutic and adverse effects | Indicated for treatment of Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis and Pathological Hypersecretory Conditions Including Zollinger Ellison Syndrome. Pantoprazole sodium is well tolerated. |
| NOAEL | 60 mg/kg/day in one-year study in dogs |

### Application of Adjustment Factors

| F1: Extrapolation between species | 2 | Based on body weight: surface area calculations for dogs, a factor of 2 is selected |
| F2: Inter-individual variability | 10 | Conventionally used to allow for differences between individuals in the human population |
| F3: Duration of toxicity | 10 | One-year toxicity study in dogs |
| F4: Severe toxicity (1-10) | 5 | Equivocal genotoxicity response and findings in stomach in repeated dose studies in rats and dogs |
| F5: NOAEL Vs LOAEL (10 if LOAEL) | 1 | NOAEL dose is selected. |

**PK correction** | 1.29 | Inhalational/oral bioavailability ratio. |
4. IDENTIFICATION OF THE ACTIVE SUBSTANCE

Pantoprazole Sodium is an organic sodium salt (salt form of a substituted benzimidazole) with proton pump inhibitor activity.

**IUPAC name:** sodium;5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl] benzimidazol-1-ide

**Chemical Abstracts Service (CAS) registry number:** 164579-32-2

**Chemical description and physical properties:**

White to off-white powder, Pantoprazole Sodium is soluble in methanol and water and practically insoluble in dichloromethane.

**Molecular weight:** 432.36 g/mol

**Molecular formula:** $C_{16}H_{14}F_{2}N_{3}NaO_{4}S$

![Structure of Pantoprazole Sodium](image)

**Figure 1:** Structure of Pantoprazole Sodium (1).
5. OBJECTIVE AND SEARCH STRATEGY

At present, pharmaceutical companies are investing significant effort to assess and control cross-contamination risk of drug products that are manufactured in the shared production facilities (2). Determination of health-based exposure limits for a residual active substance through the derivation of a safe threshold value is employed to identify the risk posed. The derivation of 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 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.

6. INTRODUCTION

Pantoprazole is a first-generation proton pump inhibitor, used to manage other disorders in which the decrease of gastric acid secretion is needed.

Pharmacotherapeutic group- proton pump inhibitors, ATC code- A02BC02 (3).

7. HAZARD IDENTIFICATION

a. Pharmacodynamic data

Pantoprazole sodium forms a covalent bond to two sites of the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell and results in dose-related suppresses the final step in gastric acid production. This leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.
In rats and mice, the long-lasting inhibition of basal and stimulated gastric acid secretion by pantoprazole sodium is demonstrated with median effective dose (ED50) values ranging from 0.2 to 2.4 mg/kg.

Following the initial oral dose of 40 mg Pantoprazole, a 51% mean inhibition of gastric acid secretion was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of Pantoprazole; there was no evidence of rebound hyper secretion.

Pantoprazole Sodium induced a dose-dependent increase in serum gastrin levels up to values above 1000 pg/ml from a control level of about 100 pg/ml (4, 5).

b. Acute toxicity studies

Acute oral and intravenous toxicity of Pantoprazole was determined in rats and mice followed by oral and intravenous administration. The LD50 values are presented in Table 1. The observed clinical signs in rats and mice were similar and 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 intravenous doses, but the survivors recovered quickly and appeared fully normal after the 2-week observation period (4).

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.

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Route</th>
<th>LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Male</td>
<td>Oral</td>
<td>&gt;1000</td>
</tr>
<tr>
<td></td>
<td>Female</td>
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</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>Oral</td>
<td>1343</td>
</tr>
</tbody>
</table>
c. Repeated dose toxicity

Repeated dose toxicity study in rodents

Repeated dose studies in rats of 1- and 6-month duration were conducted with Pantoprazole at dose levels of 1, 5, 20, and 500 mg/kg and 0.8, 4, 16 and 320 mg/kg, respectively; doses for a 1-month intravenous 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 (Tecta, product monograph, 2018). Animals were observed for mortality, clinical signs of toxicity, changes in body weight, hematology and clinical pathology evaluation, gross and histopathological examination were carried out at the end of the study period. Increased stomach weights and morphologic changes of the mucosa were observed in all studies. 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. An 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. Liver weights were increased 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. 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 study, the selected dose levels for 1- and 6-month (beagle) were 7.5, 15, 30, and 100 mg/kg and 5, 15, 30, and 60 mg/kg, respectively. In a 12-month study, the dose levels of 2.5, 15, and 60 mg/kg were used. Dose-dependent hypergastrinemia was observed at all dose levels in these studies, but was reversible upon cessation of treatment. Drug-related effects on the stomach
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included increased stomach weights and morphologic changes of the mucosa. In dogs, increased stomach weight was observed at all dose levels in all the studies. 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. Hypergastinemia and gastric changes were considered to be the consequence of the pharmacological action of the compound, namely prolonged and profound inhibition of acid secretion. An increase in 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 males and females had increased liver weights after 6 months’ administration of 30 or 60 mg/kg, but not of 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 metabolism of thyroid hormones in the liver and has been described in a similar form for other drugs. 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. Reversible increases in serum cholesterol values were observed 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.

d. Carcinogenicity
A total of three carcinogenicity studies were conducted, two with rats and one with mice (Tecta,
product monograph, 2018 and Protonix, prescribing information, 2012). In the rat study, dose levels of 0.5, 5, 50 and 200 mg/kg/day in the first study and 5, 15 and 50 mg/kg/day in the second study was used. A 24-month oral study was conducted at doses of 5, 25 and 150 mg/kg/day in B6C3F1 mouse.

In the first 2-year carcinogenicity study in 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. 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. No metastases from any gastric neuroendocrine cell tumors were detected.

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. 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. 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 dose).

e. **In-vitro and in-vivo genotoxicity**
Pantoprazole was found negative in the in-vitro studies such as Ames test, an in vivo chromosome aberration assay in rat bone marrow, a mouse lymphoma assay, 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 the in vitro human lymphocytes (4).

**f. Reproductive and developmental toxicity**

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 (4). Pantoprazole did not affect fertility in rats up to 500 mg/kg p.o. for 127 days. 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.

**g. Sensitizing potential**

Data regarding the sensitization potential of pantoprazole sodium in humans is not available.

**8. IDENTIFICATION OF CRITICAL EFFECTS**

Scientific evaluation of published pharmacological and toxicological data including clinical and non-clinical reports help to identify the adverse effect of the active substances. The critical effect of the active substance is one that meets the severity and persistence criteria at the lowest intake to define the hazard associated with the intake.
PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM

i. Most sensitive indicator of an adverse effect seen in non-clinical toxicity data

In the repeated dose toxicity studies, treatment related changes in stomach, liver and thyroid was observed in rats and dogs. Pantoprazole sodium caused neuroendocrine neoplasm in stomach and hepatocellular carcinoma in rats and mice, respectively. Equivocal response was observed in genotoxicity assays.

ii. Clinical therapeutic and adverse effects

Pantoprazole sodium for Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to Pantoprazole Sodium, Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD (gastroesophageal reflux disease) and a history of erosive esophagitis. In this multicentre, pharmacodynamic crossover study, a 40 mg oral dose of Pantoprazole Sodium for Delayed-Release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of Pantoprazole sodium Delayed-Release Tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Adverse effects: Pantoprazole is well tolerated. Most adverse events have been mild and transient showing no consistent relationship with treatment.

9. RATIONAL FOR NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) VALUE SELECTION

In the repeated dose toxicity studies, treatment related changes in stomach, liver and thyroid was observed in rats and dogs. Pantoprazole Sodium caused neuroendocrine neoplasm in stomach and hepatocellular carcinoma in rats and mice, respectively. Equivocal response was observed for genotoxicity in the in vitro and in vivo assays. The relevance of hepatocellular tumor is not known. In case of tumor in stomach, 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. Based on these observations, a NOAEL dose of 60 mg/kg/day from a one-year study in dogs was selected (4). At this dose level, there was no pulmonary edema was observed in dogs.
10. APPLICATION OF ADJUSTMENT FACTORS (RATIONALE FOR THE ADJUSTMENT FACTORS)

A series of modifying or safety factors are used when NOAEL is based on studies of differing types and duration in different species to provide a risk assessment for human exposure. These factors were generally established according to Appendices 3 of the ICH Q3C (R4) and VICH GL 18 (6, 7).

   a. F1: interspecies difference

This factor considers the comparative surface area: body weight ratios for the species concerned and for man. Surface area is calculated as \( S = K M^{0.67} \) where \( M \) is the body mass and \( K \) is constant, has been taken to be 10 according to the appendices 3 of the ICH guideline. For a 50 kg person, the equation gives a surface area of 64.3dm\(^2\); the surface area: body weight ratio is thus 2.76. The multiples of the human surface area: body weight ration gives factors for the mouse=12, rat=5, monkey=3, rabbit=2.5 and dog=2.

A factor of 2 is used because of the selection of dogs.

   b. F2: inter –individual differences

A factor of 10 is conventionally used to allow for differences between individuals in human population.

   c. F3: duration of exposure

A variable factor up to 10 is used for duration of exposure factor in the reported studies. For reproductive studies a factor of 1 is used if the whole period of organogenesis is covered. A factor of 2 is used for a 6-month study in rodents or 3.5-year study in non-rodents. A factor 5 has been used for a 3-month study in rodents or a 2-year study in non-rodents and a factor of 10 for shorter duration studies.

A factor of 10 is selected based on selection of one-year study in dogs.

   d. F4: nature of toxicity

A variable factor is applied when the toxicity produced is irreversible in nature i.e. carcinogenicity, neurotoxicity or teratogenicity. A factor of 10 is used when oncogenic or
neurotoxic responses are present. A variable factor is used for reproductive toxicity as follows for embryo or fetal toxicity or mortality associated with maternal toxicity; 5 for embryo or fetal toxicity or mortality without maternal toxicity; 5 for a teratogenic effect with maternal toxicity and 10 for a teratogenic effect in the absence of accompanying maternal toxicity.

A factor of 5 is selected for the observed genotoxicity and effect on stomach in repeated dose studies.

e. **F5: quality of data**

A factor of 1 is used because of selection of NOAEL dose.

The PDE calculation is generally presented in the format

\[
PDE \text{ (mg/day)} = \frac{\text{NOAEL (mg/kg/day)} \times \text{body weight (kg)}}{F_1 \times F_2 \times F_3 \times F_4 \times F_5}
\]

\[
60 \times 50 = \frac{2 \times 10 \times 5 \times 1 \times 1.29}{1.29} = 2.325 \text{ mg/day}
\]

**11. PK CORRECTION**

For PDE calculation, a correction factor of 1.29 (inhalational/oral) bioavailability ratio.
12. REFERENCES

1. Pantoprazole sodium, Pub chem, 2019


3. World Health Organization (WHO). ATC/DDD Index 2019
   https://www.whocc.no/atc_ddd_index/?code=A02BC02&showdescription

4. TECTA, product monograph, Submission Control Number: 213796.

   https://www.drugbank.ca/drugs/DB00213

6. ICH guideline Q3C (R7) on impurities: guideline for residual solvents,

7. VICH GL 18 residual solvents in new veterinary medicinal products, active substances and excipients (Revision), EMA/CVMP/VICH/502/1999-Rev.1, 25 May 2010
ANNEXURE I: PHARMACOKINETICS

Pantoprazole sodium is absorbed rapidly in both rat and dog. Peak plasma levels are attained within 15 to 20 minutes in the rat and after about 1 hour in the dog. Oral bioavailability is 33% in the rat and 49% in the dog. Following administration of pantoprazole sodium, distribution of radioactivity in the blood and most organs is found to be uniform initially. After 16 hours, radiolabelled pantoprazole is predominantly detected in the stomach wall. After 48 hours, all the administered radioactivity is found to have been excreted. Penetration of the blood-brain barrier by radiolabelled pantoprazole is very low. Protein binding in the rat and dog is 95% and 86%, respectively.

Pantoprazole is extensively metabolized. Oxidations and reductions at different sites of the molecule, together with Phase II reactions (sulfation and glucuronidation) and combinations thereof result in the formation of various metabolites. In rats and dogs, 29-33% of a pantoprazole sodium dose is excreted as urinary metabolites, and the remainder as biliary/fecal metabolites.

Mammoglandular passage and transplacental transport has been investigated in the rat using radiolabelled pantoprazole sodium. A maximum of 0.23% of the administered dose is excreted in the milk. Radioactivity penetrates the placenta with 0.1-0.2% of the dose /g fetal tissue on the first day after oral administration.

Maximum serum concentrations of pantoprazole magnesium are reached within approximately 2.5 hours after oral intake. Following a dose of 40 mg, mean maximum serum concentrations of approximately 1.3 μg/mL and 1.4μg/mL are reached after about 2.5 and 6 hours under fasting and fed conditions respectively. Time to reach maximum serum concentrations is slightly increased when the drug is given together with a high caloric breakfast. Considering the long duration of action of pantoprazole, which by far exceeds the time period over which serum concentrations are measurable, this observed variation in tmax is considered to be of no clinical importance.

Morning administration of pantoprazole sodium was significantly superior to evening dosing with regard to 24-hour intragastric pH, hence morning dosing should be recommended for the treatment of patients. Since the intake of the drug before a breakfast did not influence Cmax and
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AUC, which characterize rate and extent of absorption, no specific requirements for intake of pantoprazole in relation to breakfast are necessary. The absolute bioavailability of the pantoprazole sodium tablet is 77%.

Pantoprazole undergoes metabolic transformation in the liver. Approximately 82% of the oral dose is removed by renal excretion, and the remainder via feces. The main serum metabolites (M1-M3) are sulphate conjugates formed after demethylation at the pyridine moiety, the sulphoxide group being either retained (M2, main metabolite), or oxidized to a sulphone (M1), or reduced to a sulphide (M3). These metabolites also occur in the urine (main metabolite M2). Conjugates with glucuronic acid are also found in the urine.

In single dose clinical pharmacology studies, pantoprazole sodium was administered to fasting healthy volunteers concomitantly with combinations of amoxicillin, clarithromycin, and/or metronidazole. Pharmacokinetic characteristics of each of the subject medications administered alone were also evaluated as a reference point. Equivalence between the test (i.e., in combination regimen) and the respective reference was concluded when the 90% confidence interval was within the equivalence range of 0.67 to 1.50 for the AUC0-∞ and Cmax.

The potential influence of the concomitant administration of pantoprazole sodium 40 mg with clarithromycin 500 mg and metronidazole 500 mg on pharmacokinetic characteristics was evaluated following a single oral dose administered to fasted healthy volunteers. A lack of interaction was shown for each of the drugs (see Table 8 below).
ANNEXURE II: GLOSSARY

ADI: Acceptable daily intake
AUC: Area under the curve
GRAS: Generally regarded as safe
GLP: Good laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
LED: Lowest-effective dose
TDLo (Toxic Dose Low,): Lowest published toxic dose
LOAEL: Lowest-observed-adverse-effect level
LOEL: Lowest-observed-effect level
MSDS: Material safety data sheet
MTD: Maximum tolerable dose
MPDD: Maximum permissible daily dose
MTEL: Maximum tolerable exposure level
NEL: No-effect level
NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect level
OEL: Occupational exposure limit
QSAR: Quantitative structure–activity relationship
SDS: Safety data sheet
ADI: Acceptable daily intake. Estimate by JECFA; the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk.

Area under the curve (AUC): Area between a curve and the abscissa (horizontal axis), i.e., the area underneath the graph of a function; often, the area under the tissue (plasma) concentration curve of a substance expressed as a function of time.

Bioaccumulation: progressive increase in the amount of a substance in an organism or part of an organism that occurs because the rate of intake exceeds the organism’s ability to remove the substance from the body.

Bioavailability: biological and physiological availability. Extent of absorption of a substance by a living organism compared to a standard system.

Biological half-life: for a substance, the time required for the amount of that substance in a biological system to be reduced to one-half of its value by biological processes, when the rate of removal is approximately exponential.

Carcinogen: agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

Clastogen: agent causing chromosome breakage and (or) consequent gain, loss, or rearrangement of pieces of chromosomes.

Clearance: volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination.

Cmax: used in pharmacokinetics referring to the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area after the drug has been administrated and before the administration of a second dose.

Critical dose: dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ.

Critical effect: for deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ:
Adverse effects with no defined threshold concentration are regarded as critical. Dose (of a substance): total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

Draize test: evaluation of materials for their potential to cause dermal or ocular irritation and corrosion following local exposure; generally using the rabbit model (almost exclusively the New Zealand White) although other animal species have been used.

Elimination (in toxicology): disappearance of a substance from an organism or a part thereof, by processes of metabolism, secretion, or excretion.

Embryotoxicity: production by a substance of toxic effects in progeny in the first period of pregnancy between conception and the fetal stage.

Fetotoxicity: production by a substance of toxic effects in progeny in the second period of pregnancy between fetal stage and delivery.

First-pass effect: biotransformation and, in some cases, elimination of a substance in the liver after absorption from the intestine and before it reaches the systemic circulation.

Gavage: administration of materials directly into the stomach by esophageal intubation.

Generally regarded as safe (GRAS): phrase used to describe the USFDA philosophy that justifies approval of food additives that may not meet the usual test criteria for safety but have been used extensively and have not demonstrated that they cause any harm to consumers.

Genotoxic: capable of causing a change to the structure of the genome.

Good laboratory practice (GLP) principles: fundamental rules incorporated in OECD guidelines and national regulations concerned with the process of effective organization and the conditions under which laboratory studies are properly planned, performed, monitored, recorded, and reported.

Good manufacturing practice (GMP) principles: fundamental rules incorporated in national regulations concerned with the process of effective organization of production and ensuring standards of defined quality at all stages of production, distribution, and marketing.
Hazard identification: determination of substances of concern, their adverse effects, target populations, and conditions of exposure, considering toxicity data and knowledge of effects on human health, other organisms, and their environment.

Hypersensitivity: state in which an individual reacts with allergic effects following exposure to a certain substance (allergen) after having been exposed previously to the same substance.

In silico: phrase applied to data generated and analysed using computer modelling and information technology.

In vitro: in glass, referring to a study in the laboratory usually involving isolated organ, tissue, cell, or biochemical systems.

In vivo: In the living body, referring to a study performed on a living organism.

Lethal dose (LD): amount of a substance or physical agent (e.g., radiation) that causes death when taken into the body.

Lowest-effective dose (LED): lowest dose of a chemical inducing a specified effect in a specified fraction of exposed individuals.

Lowest published toxic dose (Toxic Dose Low, TDLo): the lowest dosage per unit of bodyweight (typically stated in milligrams per kilogram) of a substance known to have produced signs of toxicity in a particular animal species.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

Lowest-observed-effect level (LOEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.
PERMITTED DAILY EXPOSURE FOR PANTOPRAZOLE SODIUM


Maximum permissible daily dose (MPDD): maximum daily dose of substance whose penetration into a human body during a lifetime will not cause diseases or health hazards that can be detected by current investigation methods and will not adversely affect future generations.

Maximum tolerable dose (MTD): highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD0).

Maximum tolerable exposure level (MTEL): maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time. Maximum tolerated dose (MTD): high dose used in chronic toxicity testing that is expected on the basis of an adequate sub chronic study to produce limited toxicity when administered for the duration of the test period.

Median lethal dose (LD50): statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50% of organisms in a given population under a defined set of conditions.

Mutagenicity: ability of a physical, chemical, or biological agent to induce (or generate) heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

No-effect level (NEL): maximum dose (of a substance) that produces no detectable changes under defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure. No-observed-effect level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms.
distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Quantitative structure–activity relationship (QSAR): quantitative structure–biological activity model derived using regression analysis and containing as parameters physicochemical constants, indicator variables, or theoretically calculated values.

Safety data sheet (SDS): single page giving toxicological and other safety advice, usually associated with a particular preparation, substance, or process.

Target (in biology): any organism, organ, tissue, cell or cell constituent that is subject to the action of an agent.

Temporary acceptable daily intake: value for the acceptable daily intake proposed for guidance when data are sufficient to conclude that use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. Note: A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be available.