PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

PERMITTED DAILY EXPOSURE FOR LOPERAMIDE HCL

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 Loperamide Hydrochloride 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:

Loperamide is a synthetic opioid μ-receptor agonist, and is classified into anti-motility agent category. At the therapeutic dose level, it does not pass the blood brain barrier. The main mechanism of its anti-diarrheal action is due to the reduction of intestinal motility. Loperamide at 4 mg PO daily decreases the stool frequency and liquidity, and controls fecal urgency. It alleviates symptoms of acute and chronic diarrhea.

Common side effects include abdominal pain, constipation, sleepiness, vomiting and a dry mouth. It may increase the risk of toxic megacolon. Loperamide's safety in pregnancy is unclear, but no evidence of harm has been found. It appears to be safe in breastfeeding. It is an opioid with no significant absorption from the gut and does not cross the blood–brain barrier when used at normal doses. It works by slowing the contractions of the intestines.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

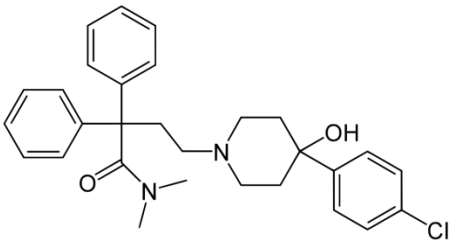
IUPAC name: 4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-N,N-dimethyl-2,2-diphenylbutanamide

Chemical Abstract Services (CAS) Registry Number: 53179-11-6

Molecular Weight: 477.037 g/mol (513.506 with HCl) g·mol−1

Chemical Formula: $C_{29}H_{33}ClN_2O_2$

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	In vitro and animal studies show that Loperamide hydrochloride acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing peristalsis, and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency. In man, Loperamide hydrochloride prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Tolerance to the antidiarrheal effect has not been observed. Clinical studies have indicated that the apparent elimination half-life of Loperamide in man is 10.8 hours with a range of 9.1 - 14.4 hours. Plasma levels of unchanged drug remain below 2 nanograms per mL after the intake of a 2mg capsule of IMODIUM®. Plasma levels are highest approximately five hours after administration of the capsule and 2.5 hours after the liquid. The peak plasma levels of Loperamide were similar for both formulations. Elimination of Loperamide mainly occurs by oxidative N-demethylation. Cytochrome P450 (CYP450) isozymes, CYP2C8 and CYP3A4, are thought to play an important role in Loperamide N-demethylation process since quercetin (CYP2C8 inhibitor) and ketoconazole (CYP3A4 inhibitor) significantly inhibited the Ndemethylation process in vitro by 40% and 90%, respectively. In addition, CYP2B6 and CYP2D6 appear to play a minor role in loperamide N-demethylation. Excretion of the unchanged Loperamide and its metabolites mainly occurs through the feces. In those patients in whom biochemical and hematological parameters were monitored during clinical trials, no trends toward abnormality during IMODIUM® therapy were noted. Similarly, urinalyses, EKG and clinical ophthalmological examinations did not show trends toward abnormality.
Pharmacokinetics data	**Absorption:** Plasma concentrations of unchanged drug remain below 2 ng/ml after the intake of a 2 mg Loperamide hydrochloride capsule. Plasma concentrations are highest approximately 5 hours after administration of the capsule and 2.5 hours after the liquid. The peak plasma concentrations of Loperamide were similar for both formulations. **Distribution**: Based on literature information, the plasma protein binding of Loperamide is about 95%. Loperamide is a P-glycoprotein substrate. **Elimination**: The apparent elimination half-life of Loperamide is 10.8 hours with a range of 9.1 to 14.4 hours. Elimination of Loperamide mainly occurs by oxidative N-demethylation.

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Case Study 1:

Species	Route	End point	Dose (mg/kg)
Rat	Oral	LD50	185
Mouse	Oral	LD50	105

Case Study 2:

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Rat	LD50	Oral	98	Null	Drug Development Research., 8(279), 1986
Rat	LD50	Intravenous	5.09	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Mouse	LD50	Oral	105	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Mouse	LD50	Intraperitoneal	28	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Mouse	LD50	Subcutaneous	75	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Dog	LD50	Oral	40	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Dog	LD50	Intravenous	2.8	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981
Guinea pig	LD50	Oral	42	Sense organs and special senses: ptosis: eye; behavioral: tremor	Pharmacological and Biochemical Properties of Drug Substances., 3(461), 1981

Laboratory Animals: Acute Exposure/ The intravenous injection of loperamide induced an immediate fall in blood pressure and heart rate in anesthetized rats. Both effects were inhibited by the opiate antagonists naloxone and MRZ 2266 BS. Bilateral vagotomy also inhibited both effects whereas atropine only reduced the bradycardia, but the combination of atropine and tertatolol suppressed the bradycardia. A high dose of loperamide induced bradycardia in pithed rats. This effect was prevented by MRZ 2266 BS but not by naloxone. It is concluded that loperamide can elicit a vagally mediated reflex involving vagal and sympathetic mechanisms and could stimulate cardiac opiate receptors, probably kappa, both effects leading to bradycardia.

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SUMMARY OF HAZARD IDENTIFICATION:

Human Exposure Studies: This crossover, double-blind study investigated the effects of single oral doses of the prodrug loperamide oxide, which is reduced gradually to loperamide in the intestine, and loperamide on jejunal motor activity in 12 fasting healthy men. Five minutes after a phase III of the migrating motor complex (MMC), 2 mg loperamide oxide, 4 mg loperamide oxide, 4 mg loperamide, or placebo were administered. Thereafter, motor activity 10-30 cm abroad the ligament of Treitz was recorded with five catheter orifices at 3-cm intervals over 4 hr. Number of contractions and area under curve increased significantly with 4 mg loperamide and 4 mg loperamide oxide, the increases with loperamide oxide occurring more gradually. Placebo and 2 mg loperamide oxide had no discernible effects. With both 4 mg loperamide and 4 mg loperamide oxide, phase I of the MMC was slightly prolonged and phase II and the time from drug administration to the onset of the first phase III slightly shortened. The percentage of aborally propagated contractions in phase II increased with all active treatments, whereas the occurrence of phases III was not altered.

Human Exposure Studies: Loperamide (LOP) is an anti-diarrheal agent which is thought to act largely by slowing transit with an uncertain effect on the fluid content of the small and large bowel in humans.
Adding simethicone (SIM) to LOP improves its efficacy, but the mechanism of interaction is unclear. Novel MRI techniques to assess small bowel water content (SBWC) have shown that mannitol solutions markedly increase SBWC and can be used as a model of diarrhea. We aimed to use quantitative MRI techniques to compare the actions in the gut of LOP and LOP + SIM in a model of secretory diarrhoea using mannitol. A total of 18 healthy volunteers ingested capsules containing placebo (PLA) or 12 mg LOP or 12 mg LOP + 125 mg SIM. After 100 min they were given a drink containing 5% mannitol in 350 mL of water. They underwent baseline fasting and postprandial serial MRI scans at 45 min intervals for 4.5 h after ingesting the drink. A range of MRI sequences was acquired to image the gut. LOP and LOP + SIM significantly accelerated gastric emptying ($p < 0.03$) and reduced SBWC during the late phase (135-270 min after mannitol ingestion), $p < 0.009$, while delaying arrival of fluid in the ascending colon (AC). The relaxation time T2 of the contents of the AC was reduced by both drugs ($p < 0.0001$). LOP and LOP + SIM accelerate gastric emptying, but reduce small bowel water content which may contribute to the delay in oral-caecal transit and overall anti-diarrheal effect.

Human Exposure Studies: Previous work in our laboratory has found that mild physical activity accelerates mouth-to-large intestinal transit of lactulose in a mixed liquid meal. Because loperamide is commonly used as an antidiarrheal agent, we wondered if it would blunt the orocecal transit acceleration provoked by mild exercise. We investigated this equation in 12

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SUMMARY OF HAZARD IDENTIFICATION:	
	healthy persons by comparing orocolonic liquid transit at rest and in mild exercise. Each subject ingested 8 mg loperamide 1 hr prior to study under both resting and exercise conditions. With loperamide treatment, exercise (walking at 5.6 km/hr) failed to hasten increased H2 excretion (mean transit time 72 +/- 12 min at rest, 90 +/- 15 min in exercise; p = NS). This result contrasts sharply with previously reported controls: loperamide completely abolished exercise-induced orocecal transit acceleration (-23 +/- 5 min in controls; +18 +/- 13 min with loperamide; $p < 0.05$). Compared with these same controls, resting transit was not significantly slowed by the drug, while transit in exercise was retarded (64 +/- 5 min in controls, 90 +/- 15 min with loperamide; p = 0.06). Loperamide left unchanged the heart rate and oxygen uptake rises associated with exercise. In summary, by showing that loperamide blocks an exercise effect on the upper gut, these results suggest that the drug might prove effective in treating some gut symptoms induced by physical activity.
Repeated Dose Toxicity (Chronic Toxicity)	**Laboratory Animals:** Subchronic or Prechronic Exposure/Wistar rats (10 males and 10 females per dose group) were given Loperamide in their diet at 40, 10 and 2.5 mg/100 g of food seven days a week for **15 weeks**. Control animals received diet only. No drug-induced mortality was observed. Health, behavior and appearance were normal in all groups, except that the 40 mg/100 g food-dosed animals showed a swollen abdomen during the first four weeks. No effects could be detected on hemograms, serum analyses and urinalyses except a decrease of creatinine in the dosed animals. Weight gain and food consumption were lower in the 40 mg/100 g food-dosed animals. At this 40 mg/100 g food dose, some minor macroscopic and microscopic changes are probably related to reduced food consumption. **Laboratory Animals**: Chronic Exposure or Carcinogenicity/ Beagle dogs (3 males and 3 females per dose group) were given Loperamide in gelatin capsules at 5.0, 1.25 and 0.31 mg/kg six days a week for **12 months**. Some depression was seen during the first week of drug administration at 1.25 and 5 mg/kg. Behavior and appearance were normal during the rest of the experiment, except that hemorrhagic stools were seen from time to time at 5 mg/kg and soft stools at 0.31 and 1.25 mg/kg, especially during the first 6 weeks of drug administration. Blood pressure, heart rate, electrocardiogram, hemograms, serum analysis and urinalysis were normal throughout the experiment. Gross pathologic and histologic examinations failed to reveal any dose or drug-related changes. The long-term toxicologic study of Loperamide that dog was carried out **12 months** and rat was carried out 18 months shows, when dosage increases to 5 mg/kg/day (30 times to the maximum consumption of human body) and 40 mg/kg/day (240 times to the maximum consumption of human body), occur some body weight increments minimizings and food consumption quantity increase respectively, do not find other toxic action in addition. Result of study shows that the non-toxic reaction dosage level (NTEL) to dog and rat is

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SUMMARY OF HAZARD IDENTIFICATION:

respectively 1.25 mg/kg/day (8 times to the maximum consumption of human body) and 10 mg/kg/day (60 times to the maximum consumption of human body). Show Loperamide hereditary-less toxicity, non-carcinogenesis with external special toxicologic study result in the body.

Carcinogenicity

Duration	Species	Route	Dose (mg/kg)	End Point	Effects
18 months	Rat	Oral	32	NOEL	Not Carcinogenic

In an **18-month rat** study with oral doses up to 40 mg/kg/day (21 times the maximum human dose of 16 mg/day, based on a body surface area comparison), there was no evidence of carcinogenesis.

Laboratory Animals: Chronic Exposure or Carcinogenicity/ In a study in rats using Loperamide dosages up to 133 times the maximum human dosage (on a mg/kg basis) for **18 months**, there was no evidence of carcinogenicity.

In vivo/In vitro Genotoxicity Studies

Study Type	Cell Type/Organism	Results
Bacterial Mutagenicity (Ames)	Salmonella	Negative

Loperamide was not genotoxic in the Ames test, the SOS chromotest in E. coli, the dominant lethal test in female mice, or the mouse embryo cell transformation assay.

Reproductive/Developmental Toxicity

Study Type	Species	Route	Dose (mg/kg)	End point	Effects
Reproductive & Fertility	Rat	Oral	12	LOEL	Fertility
Fertility and Embryonic Development	Rat	Oral	2.4	NOEL	Not Teratogenic
Fertility and Embryonic Development	Rabbit	Oral	2.4	NOEL	Not Teratogenic

Fertility and reproductive performance was evaluated in rats using oral doses of 2.5, 10, and 40 mg/kg/day in one study, and 1, 5, 10, 20, and 40 mg/kg/day (females only) in a second study. Oral administration of 20 mg/kg/day (approximately 11 times the human dose based on a body surface area comparison) and higher produced strong impairment of female fertility. Treatment of female rats with up to 10 mg/kg/day p.o. (approximately 5 times the human dose based on a body surface area comparison) had no effect on fertility. Treatment of male rats with 40 mg/kg/day p.o. (approximately 21 times the human dose based on a body surface area comparison) produced impairment of male fertility, whereas administration of up to 10 mg/kg/day (approximately 5 times the human dose based on a body surface area comparison) had no effect.

Teratogenic Effects: Pregnancy Category C Teratology studies have been performed in rats using oral doses of 2.5, 10, and 40 mg/kg/day, and in rabbits using oral doses of 5, 20, and 40 mg/kg/day. These studies have revealed no evidence of impaired fertility or harm to the fetus at doses up to 10 mg/kg/day in rats (5 times the human dose based on body surface area comparison) and 40 mg/kg/day in rabbits (43 times the human dose based on body surface area comparison). Treatment of rats with 40 mg/kg/day p.o. (21 times the human

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SUMMARY OF HAZARD IDENTIFICATION:	
	dose based on a body surface area comparison) produced marked impairment of fertility. The studies produced no evidence of teratogenic activity. There are no adequate and well-controlled studies in pregnant women. Loperamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Highly Sensitizing Potential	Skin sensitivity potential is not known.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effect	**Adults:** The recommended initial dose is 4mg (two capsules) followed by 2 mg (one capsule) after each unformed stool. Daily dose should not exceed 16mg (eight capsules). Clinical improvement is usually observed within 48 hours. **Adverse effects:** Bloating, Constipation, Loss of Appetite, stomach pain (severe) with nausea and vomiting.

NOAEL/LOAEL	0.04 mg/kg is the NOAEL value selected from minimum daily dose.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	For extrapolation from humans to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	2	3 months duration study in rodent (15 weeks).
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.04 (NOAEL) x 50}}{\text{1 x 10 x 2 x 1 x 5}}$ = 0.02 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Loperamide.
- https://www.pfizer.com/files/products/material_safety_data/LOPERAMIDE%20HYDROCHLORIDE%202MG%20HARD%20CAPSULES.
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/017694s050lbl.

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- https://pubchem.ncbi.nlm.nih.gov/compound/Loperamide#section=Non-Human-Toxicity-Values
- https://www.drugs.com/pro/loperamide.html