PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

PERMITTED DAILY EXPOSURE FOR PREGABALIN

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 Pregabalin 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:

Pregabalin is a medication used to treat epilepsy, neuropathic pain, fibromyalgia, restless leg syndrome, and generalized anxiety disorder. Its use in epilepsy is as an add-on therapy for partial seizures. When used before surgery, it reduces pain but results in greater sedation and visual disturbances. It is taken by mouth.

Common side effects include headache, dizziness, sleepiness, confusion, trouble with memory, poor coordination, dry mouth, problem with vision, and weight gain. Serious side effects may include angioedema, drug misuse, and an increased suicide risk. When Pregabalin is taken at high doses over a long period of time, addiction may occur, but if taken at usual doses the risk is low. Use during pregnancy or breastfeeding is of unclear safety. Pregabalin is a gabapentinoid and acts by inhibiting certain calcium channels.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Pregabalin is a white to off-white, crystalline solid with a pKa1 of 4.2 and a pKa2 of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions.

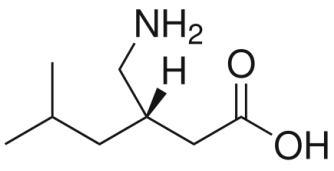
IUPAC name: (3S)-3-(amino methyl)-5-methylhexanoic acid

Chemical Abstract Services (CAS) Registry Number: 148553-50-8

Molecular Weight: 159.229 g/mol g·mol−1

Chemical Formula: $C_8H_{17}NO_2$

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	Although the structure of Pregabalin is similar to gamma-aminobutyric acid (GABA), it does not bind to GABA receptors. Instead, it binds the alpha2-delta subunit of presynaptic voltage-gated calcium channels in the central nervous system. Pregabalin does not modulate dopamine receptors, serotonin receptors, opiate receptors, sodium channels or cyclooxygenase activity.
Pharmacokinetics data	**Absorption:** After oral dosing administered in the fasted state, Pregabalin absorption is rapid, and extensive. Pregabalin oral bioavailability is reported to be ≥90% regardless of the dose. Cmax is attained within 1.5 hours after single or multiple doses, and steady state is attained within 24-48 hours with repeated administration. Both Cmax and AUC appear to be dose proportional. Food decreases the rate of Pregabalin absorption and as a result, lowers the Cmax by an estimated 25-30% and increases the Tmax to approximately 3 hours. However, the effect of food does not appear to impact the total absorption of Pregabalin in a way that is clinically relevant. As a result, Pregabalin can be administered with or without food. **Distribution:** After oral administration of Pregabalin, the reported apparent volume of distribution is roughly 0.5 L/kg. Although Pregabalin is not very lipophilic, it is able to cross the blood brain barrier (BBB). System L transporters facilitate the transport of large amino acids across the BBB and it has been confirmed that Pregabalin is a substrate. This information suggests that system L transporters are responsible for Pregabalin uptake into the BBB. In rat models, Pregabalin has been shown to cross the placenta **Protein Binding:** Pregabalin is not plasma protein bound. **Metabolism:** Less than 2% of Pregabalin is metabolized and it is excreted virtually unchanged in the urine **Route of Elimination:** Pregabalin is almost exclusively eliminated in the urine. Further, based on preclinical studies, Pregabalin does not appear to undergo racemization to the R enantiomer in the body.
Acute Toxicity	The most common symptoms of Pregabalin toxicity (dose range includes 800 mg/day and single doses up to 11,500 mg) include somnolence, confusion, restlessness, agitation, depression, affective disorder and seizures

Species	Route	End Point	Dose (mg/kg)
Rat	i.v.	LD50	>3000
Mouse	Oral	LD50	>5000
Rat	Oral	LD50	>5000

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Duration	Species	Route	Dose (mg/kg/day)	End Point	Target Organ
13 weeks	Rat	Oral	50	NOAEL	Central nervous system, Male reproductive system
4 weeks	Rat	Oral	500	LOAEL	Central nervous system, Male reproductive system
4 weeks	Monkey	Oral	100	NOAEL	Central Nervous System
52 weeks	Rat	Oral	50	LOAEL	Blood forming organs

Dermatopathy: Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with Pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions: Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma Pregabalin exposures (AUC) greater than or equal to 2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

Carcinogenicity

Duration	Species	Route	Dose (mg/kg/day)	End Point	Effect
104 weeks	Mouse	Oral	1000	NOAEL	Not carcinogenic
104 weeks	Rat	Oral	450	NOAEL	Not carcinogenic
104 weeks	Mouse	Oral	200	NOAEL	Malignant tumors

Dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma Pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. In an investigative study in female B6C3F1 mice, chronic treatment (24 months) with Pregabalin at 1000 mg/kg caused an increased incidence of hemangiosarcoma, consistent with previous studies, but not at 50 or 200 mg/kg. Discontinuation of treatment after 12 months at 1000 mg/kg did not significantly reduce the incidence of hemangiosarcoma at 24 months. Evidence of carcinogenicity was not seen in two studies in Wistar rats following dietary administration of Pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance in humans of this finding in mice is unknown.

In vivo/In vitro Genotoxicity Studies

Study Type	Cell Type/Organism	Result
Bacterial Mutagenicity (Ames)	Bacteria	Negative
In Vivo Unscheduled DNA	Rat	Negative

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SUMMARY OF HAZARD IDENTIFICATION:

Synthesis		
In Vivo Micronucleus	Mouse	Negative
In Vitro Chromosome Aberration	Chinese Hamster Ovary (CHO) cells	Negative

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Reproductive/Developmental Toxicity

Study type	Species	Route	Dose (mg/kg/day)	End Point	Effect
Peri-/Postnatal Development	Rat	Oral	100	NOAEL	Developmental toxicity, Fertility
Fertility & Early Embryonic Development	Rat	Oral	250	NOAEL	No effects at maximum dose
Fertility & Embryonic Development	Rat	Oral	1250	NOAEL	Negative
Embryo/ Fetal Development	Rat	Oral	500	NOAEL	Not Teratogenic
Embryo/ Fetal Development	Rabbit	Oral	500	NOAEL	Not Teratogenic

Pregnancy Category C: Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given Pregabalin during pregnancy, at doses that produced plasma Pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given Pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle

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SUMMARY OF HAZARD IDENTIFICATION:	
	responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. Use of Pregabalin during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labour & Delivery:** The effects of Pregabalin on labor and delivery in pregnant women are unknown. In the prenatalpostnatal study in rats, Pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure (AUC (0–24) of 123 µg·hr/mL) at the maximum recommended clinical dose of 600 mg/day. **Nursing Mother:** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Highly Sensitizing Potential	**Dermatopathy:** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with Pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular Lesions:** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma Pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Skin lesions & Ocular lesions observed as an adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	**Usual Adult Dose for Diabetic Neuropathy** **Immediate-release:** Initial dose: 50 mg orally 3 times a day Maximum dose: 300 mg per day **Extended-release:** Initial dose: 165 mg orally once a day after the evening meal Maximum dose: 330 mg per day **Usual Adult Dose for Post herpetic Neuralgia** **Immediate-release:**

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	Initial dose: 150 to 300 mg orally per day in 2 or 3 divided doses Maximum dose: 600 mg per day Extended-release: Initial dose: 165 mg orally once a day after the evening meal Maximum dose: 660 mg per day **Usual Adult Dose for Epilepsy** Initial dose: 150 mg orally per day in 2 or 3 divided doses Maximum dose: 600 mg per day **Usual Adult Dose for Fibromyalgia** Initial dose: 75 mg orally twice a day Maximum dose: 450 mg per day **Usual Adult Dose for Neuropathic Pain** Initial dose: 75 mg orally twice a day Maximum dose: 600 mg per day **Adverse effects:** Most common adverse reactions (≥ 5% and twice placebo) are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and thinking abnormal (primarily difficulty with concentration/attention).

NOAEL/LOAEL	NOAEL observed 50 mg/kg/day from 13 weeks study in Rats.

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	13 weeks study in rodent.
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 (50 mg/kg/day from 13 weeks study in Rats.).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

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

5. REFERENCES:

- https://en.wikipedia.org/wiki/Pregabalin.
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