PERMITTED DAILY EXPOSURE FOR LEVETIRACETAM

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 Levetiracetam 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:

Levetiracetam is a medication used to treat epilepsy. It is used for partial onset, myoclonic, or tonic-clonic seizures. It is taken by mouth as an immediate or extended release formulation or by injection into a vein.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

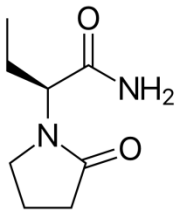
IUPAC name: (S)-2-(2-Oxopyrrolidin-1-yl)butanamide

Chemical Abstract Services (CAS) Registry Number: 5284583

Molecular Weight: 170.209 g/mol g·mol−1

Chemical Formula: $C_8H_{14}N_2O_2$

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	The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain. In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepin es, GABA (gammaaminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, in vitro studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, in vitro studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells. A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.
Pharmacokinetics data	**Absorption and Distribution:** Absorption of Levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of Levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of Levetiracetam but it decreases C_{max} by 20% and delays Tmax by 1.5 hours. The pharmacokinetics of Levetiracetam are linear over the dose range of 500 to 5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. **Metabolism:** Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-

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oxopyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of Levetiracetam or its major metabolite.

Elimination:
Levetiracetam plasma half-life in adults is 7±1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 ml/min/kg and the renal clearance is 0.6 ml/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 ml/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function [see Use in Specific Populations (8.6) and Dosage and Administration (2.5)].

Acute Toxicity

Organism	Test type	Route	Dose	Effect	Reference
Rat	LD50	Intravenous	1038 mg/kg (1038 mg/kg)	Null	United States Patent Document., #4696943
Mouse	LD50	Intravenous	1081 mg/kg (1081 mg/kg)	Null	United States Patent Document., #4696943
Rat	LD50	Oral	>5000 mg/kg	Null	Sandoz (Keppra)
Rat	LD50	Para-periosteal	>1000 mg/kg	Null	Sandoz (Keppra)

The single-dose studies in mice, rats and dogs indicate a low acute toxicity potential. Lethality was only reached after iv dosing in these studies; although in a subsequent study in mice (micronucleus test), lethality was reached at 10000 mg/kg orally. Oral administration is associated with only transient clinical signs (emesis, salivation, tremors, decreased motor activity, ataxia, tachypnea and side lying). In dogs, emesis is a dose limiting effect.

Repeated Dose Toxicity (Chronic Toxicity)

Duration	Species	Route	Dose	End Point	Target
6 months	Rat	Oral	>50 mg/kg/day	LOAEL	Liver, Kidney, Central Nervous system

Repeat administration of Levetiracetam is well tolerated. Mortality is observed only following iv administration of 900 mg/kg in rats. In general, clinical signs are minimal across studies and species with the most consistent observations being neuromuscular effects, salivation, and emesis in dogs. In the rodent only, treatment related changes in the liver and kidney were reported. In the liver, a reversible increase in liver weight and hypertrophy of centrilobular hepatocytes was observed in both sexes in rats and mice. Centrilobular vacuolation associated with lipid deposition occurred in male rats and in mice. Kidney pathology consisting of hyaline droplet nephropathy, exacerbation of chronic progressive nephropathy and associated changes was observed in male rats.
These changes are considered to be a male rat-specific pathology associated with α2- microglobulin accumulation in the proximal tubules that is not toxicologically relevant to man. There was no target organ identified in the dog. **No lethality, organ failure or other irreversible toxicity was observed after long-term (52 weeks) oral treatment up to 1800 mg/kg/day in the rat, 960 mg/kg/day in the**

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mouse and 1200 mg/kg/day in the dog.

Carcinogenicity

Duration	Species	Route	Dose	End Point
80 weeks	Mouse	Oral	Not specified	Not carcinogenic
104 weeks	Rat	Oral	1800 mg/kg/day	NOAEL (Not Carcinogenic)

Rats were dosed with Levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received Levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on mg/m^2 or exposure basis). Although **no evidence for carcinogenicity** was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

In vivo/In vitro Genotoxicity Studies

Study Type	Cell/Type/Organism	Result
In vitro	Bacterial Mutagenicity (Ames) *Salmonella*	Negative
In vitro	HGPRT Forward Gene Mutation Assay Chinese Hamster Ovary (CHO) cells	Negative
In vitro	Chromosome Aberration Chinese Hamster Ovary (CHO) cells	Negative
In vitro	Micronucleus Mouse	Negative

Levetiracetam was not mutagenic in the Ames test or in mammalian cells in vitro in the Chinese hamster ovary/HGPRT locus assay. **It was not clastogenic** in an in vitro analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an in vivo mouse micronucleus assay. The hydrolysis product and major human metabolite of **Levetiracetam was not mutagenic** in the Ames test or the in vitro mouse lymphoma assay.

Reproductive/Developmental Toxicity

Duration	Species	Route	Dose	End Point	Effect
Embryo/Fetal Development	Rat	Oral	70 mg/kg/day	NOEL	Fetotoxicity, Embryotoxicity
Embryo/Fetal Development	Rabbit	Oral	200 mg/kg/day	NOAEL	Embryotoxicity, Fetotoxicity, Maternal Toxicity
Peri-/Postnatal Development	Rat	Oral	Dose not specified	-	No effects at maximum dose

Impairment of fertility **No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day** (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis)

Pregnancy Category C: In animal studies, Levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or post natally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on mg/m^2 basis). There was no overt

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	maternal toxicity at the doses used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofoetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/d ay. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a do se of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).
Highly Sensitizing Potential	**Dermatologic Reactions:** Serious dermatologic reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), reported. Median time to onset usually 14–17 days, but may occur months after initiation of therapy.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No lethality, organ failure or other irreversible toxicity was observed after long-term (52 weeks) oral treatment up to 1800 mg/kg/day in the rat, 960 mg/kg/day in the mouse and 1200 mg/kg/day in the dog.
Clinical therapeutic and adverse effects	**Immediate-release Tablets:** Administer twice daily without regard to meals. Swallow tablets whole; do not chew or crush. **Extended-release Tablets:** Administer once daily. Swallow tablets whole; do not chew, break, or crush.

NOAEL/LOAEL	1800 mg/kg/day in Rat for 104 weeks is considered as NOAEL value.

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)	2	6 Months study in rodent.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	10	50 mg/kg/day considered as LOAEL value in rats for 6 months study.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

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CALCULATION	
PDE Calculation	NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg) F1 x F2 x F3 x F4 x F5 = 50 (LOAEL) x 50 5 x 10 x 2 x 1 x 10 = 2.5 mg/day

5. REFERENCES:

- https://pdf.hres.ca/dpd_pm/00042224.PDF
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021035s078s080,021505s021s024lbl.pdf
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Levetiracetam%20Product%20Monograph.pdf
- https://northamerica.covetrus.com/content/sds/062280.pdf