PERMITTED DAILY EXPOSURE FOR GABAPENTIN

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 Gabapentin 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:

Gabapentin is an anti-epileptic drug, also called an anticonvulsant. It affects chemicals and nerves in the body that are involved in the cause of seizures and some types of pain.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

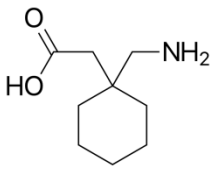
IUPAC name: 1-(Aminomethyl) cyclohexaneacetic acid

Chemical Abstract Services (CAS) Registry Number: 60142-96-3

Molecular Weight: 171.240 g·mol−1

Chemical Formula: $C_9H_{17}NO_2$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Gabapentin is a gabapentinoid, or a ligand of the auxiliary α2δ subunit site of certain voltage-dependent calcium channels (VDCCs), and thereby acts as an inhibitor of α2δ subunit-containing VDCCs. There are two drug-binding α2δ subunits, α2δ-1 and α2δ-2, and gabapentin shows similar affinity for (and hence lack of selectivity between) these two sites. Gabapentin is selective in its binding to the α2δ VDCC

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SUMMARY OF HAZARD IDENTIFICATION:	
	subunit. Despite the fact that gabapentin is a GABA analogue, and in spite of its name, it does not bind to the GABA receptors, does not convert into GABA or another GABA receptor agonist in vivo, and does not modulate GABA transport or metabolism. There is currently no evidence that the effects of gabapentin are mediated by any mechanism other than inhibition of α2δ-containing VDCCs. In accordance, inhibition of α2δ-1-containing VDCCs by gabapentin appears to be responsible for its anticonvulsant, analgesic, and anxiolytic effects. The endogenous α-amino acids L-leucine and L-isoleucine, which closely resemble gabapentin and the other gabapentinoids in chemical structure, are apparent ligands of the α2δ VDCC subunit with similar affinity as the gabapentinoids (e.g., IC50 = 71 nM for L-isoleucine), and are present in human cerebrospinal fluid at micromolar concentrations (e.g., 12.9 μM for L-leucine, 4.8 μM for L-isoleucine). It has been theorized that they may be the endogenous ligands of the subunit and that they may competitively antagonize the effects of gabapentinoids. In accordance, while gabapentinoids like gabapentin and pregabalin have nanomolar affinities for the α2δ subunit, their potencies in vivo are in the low micromolar range, and competition for binding by endogenous L-amino acids has been said to likely be responsible for this discrepancy.
Pharmacokinetics data	**Absorption:** Gabapentin is absorbed from the intestines by an active transport process mediated via the large neutral amino acid transporter 1 (LAT1, SLC7A5), a transporter for amino acids such as L-leucine and L-phenylalanine. Very few (less than 10 drugs) are known to be transported by this transporter. Gabapentin is transported solely by the LAT1, and the LAT1 is easily saturable, so the pharmacokinetics of gabapentin are dose-dependent, with diminished bioavailability and delayed peak levels at higher doses. Gabapentin enacarbil is transported not by the LAT1 but by the monocarboxylate transporter 1 (MCT1) and the sodium-dependent multivitamin transporter (SMVT), and no saturation of bioavailability has been observed with the drug up to a dose of 2,800 mg. The oral bioavailability of gabapentin is approximately 80% at 100 mg administered three times daily once every 8 hours, but decreases to 60% at 300 mg, 47% at 400 mg, 34% at 800 mg, 33% at 1,200 mg, and 27% at 1,600 mg, all with the same dosing schedule. Food increases the area-under-curve levels of gabapentin by about 10%. Drugs that increase the transit time of gabapentin in the small intestine can increase its oral bioavailability; when gabapentin was co-administered with oral morphine (which slows intestinal peristalsis), the oral bioavailability of a 600 mg dose of gabapentin increased by 50%. The oral bioavailability of gabapentin enacarbil (as gabapentin) is greater than or equal to 68%, across all doses assessed (up to 2,800 mg), with a mean of approximately 75%. Gabapentin at a low dose of 100 mg has a Tmax (time to peak levels) of approximately 1.7 hours, while the Tmax increases to 3 to 4 hours at higher doses. Food does not significantly affect the Tmax of gabapentin

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SUMMARY OF HAZARD IDENTIFICATION:

and increases the Cmax of gabapentin by approximately 10%. The Tmax of the instant-release (IR) formulation of gabapentin enacarbil (as active gabapentin) is about 2.1 to 2.6 hours across all doses (350–2,800 mg) with single administration and 1.6 to 1.9 hours across all doses (350–2,100 mg) with repeated administration. Conversely, the Tmax of the extended-release (XR) formulation of gabapentin enacarbil is about 5.1 hours at a single dose of 1,200 mg in a fasted state and 8.4 hours at a single dose of 1,200 mg in a fed state.

Distribution:

Gabapentin crosses the blood–brain barrier and enters the central nervous system. However, due to its low lipophilicity, Gabapentin requires active transport across the blood–brain barrier. The LAT1 is highly expressed at the blood–brain barrier and transports gabapentin across into the brain. As with intestinal absorption of gabapentin mediated by LAT1, transportation of gabapentin across the blood–brain barrier by LAT1 is saturable. It does not bind to other drug transporters such as P-glycoprotein (ABCB1) or OCTN2 (SLC22A5). Gabapentin is not significantly bound to plasma proteins (<1%).

Metabolism:

Gabapentin undergoes little or no metabolism. Conversely, gabapentin enacarbil, which acts as a prodrug of gabapentin, must undergo enzymatic hydrolysis to become active. This is done via non-specific esterases in the intestines and to a lesser extent in the liver.

Elimination:

Gabapentin is eliminated renally in the urine. It has a relatively short elimination half-life, with a reported value of 5.0 to 7.0 hours. Similarly, the terminal half-life of gabapentin enacarbil IR (as active gabapentin) is short at approximately 4.5 to 6.5 hours.[102] The elimination half-life of gabapentin has been found to be extended with increasing doses; in one series of studies, it was 5.4 hours for 200 mg, 6.7 hours for 400 mg, 7.3 hours for 800 mg, 9.3 hours for 1,200 mg, and 8.3 hours for 1,400 mg, all given in single doses. Because of its short elimination half-life, gabapentin must be administered 3 to 4 times per day to maintain therapeutic levels. Conversely, gabapentin enacarbil is taken twice a day and gabapentin XR (brand name Gralise) is taken once a day.

Acute Toxicity

Species	Route	End Point	Dose (mg/kg)
Mouse	Oral	LD50	>5000
Rat	Oral	LD50	>5000
Rat	i.v.	LD50	>2000
Mouse	i.v.	LD50	1000-2000
Rat	Subcutaneous	LD50	>4000

Gabapentin exhibited a very low order of acute toxicity in rodents and monkeys. In adult and 3 week old mice, no deaths occurred and median lethal doses (MLD's) were not identified, being greater than 8000, 2000, and 4000 mg/kg by the oral, intravenous, and subcutaneous routes, respectively. In adult and 3 week old rats, MLD's after single oral and intravenous doses were greater than 8000 and 2000 mg/kg, respectively.

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SUMMARY OF HAZARD IDENTIFICATION:

No signs of toxicity were noted in monkeys given single oral doses of gabapentin up to 1250 mg/kg.

Repeated Dose Toxicity (Chronic Toxicity)

Duration	Species	Route	Dose (mg/kg/day)	End Point	Target Organ
52 weeks	Rat	Oral	250	LD50	Live, Kidney
52 weeks	Monkey	Oral	250	LD50	None identified
13 weeks	Mouse	Oral	1000	LD50	No effect at maximum dose

Multidose oral administration of gabapentin was well tolerated in all specie tested (mice, rats, dogs, monkeys). Decreased body weight gain was observed in rats; hypoactivity, emesis, and salivation were observed in dogs; and changes in fecal consistency were noted in all species except mice. Increased kidney weights in male rats correlated with the accumulation of hyaline droplets in renal proximal tubular epithelium. No changes were found in the kidneys of female rats. Reversible increases in liver weight were observed in rats administered gabapentin at 3000 mg/kg for 13 weeks or 1500 mg/kg for 26 weeks, and in dogs at 2000 mg/kg for 6 months. **No pathologic findings were noted in mice given up to 2000 mg/kg gabapentin for 13 weeks or in monkeys given up to 500 mg/kg for 52 weeks.** In rats, plasma gabapentin concentrations increased with increasing dose. The increases were not dose proportional between 2000 and 3000 mg/kg, suggesting saturation of absorption at high doses.

Carcinogenicity

Duration	Species	Route	Dose (mg/kg/day)	End Point	Effect
2 Year	Mouse	Oral	2000	NOEL	Not Carcinogenic
2 Year	Male Rat	Oral	1000	NOEL	Malignant Tumors, Pancreas

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose, but not in female rats or in mice of either sex. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg are 20 times higher than the therapeutic concentrations in humans given 1200 mg/day and are 14 times higher than the therapeutic concentrations in humans given 2400 mg/day. The pancreatic acinar cell tumours in male rats are low grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. Furthermore, higher concentrations of gabapentin in pancreas relative to plasma have been observed in rats but not monkeys, which may account for the species-specific effects. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear, as the biologic characteristics of the tumours in rats are unlike those observed in humans. Ductal carcinoma comprise over 90% of all primary cancers of human exocrine pancreas, whereas acinar cell adenomas represent the primary pancreatic exocrine tumours in rats. In humans, pancreatic neoplasia exhibit local and distant tumour spread at the time of diagnosis. Metastasis occurs in 67% of cases, and survival is between 2 and 6 months after diagnosis. In contrast, pancreatic acinar cell tumours in male rats given gabapentin did not metastasize, exhibit aggressive behaviour or affect survival.

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SUMMARY OF HAZARD IDENTIFICATION:

In vivo/In vitro Genotoxicity Studies

Study Type	Cell Type/Organism	Result
Bacterial Mutagenicity (Ames test)	Salmonella, E. coli	Negative
In Vitro Chromosome Aberration	Hamster Lung Cells	Negative
In Vivo Unscheduled DNA Synthesis	Rat Hepatocyte	Negative
In Vivo Chromosome Aberration	Hamster Bone Marrow	Negative

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation in the bone marrow of hamsters.

Reproductive/Developmental Toxicity

Study Type	Species	Route	Dose (mg/kg/day)	End Point	Effect
Reproductive & Fertility	Rat	Oral	500	NOAEL	Negative
Embryo/Fetal Development	Mouse	Oral	3000	NOAEL	No effects at maximum dose
Embryo/Fetal Development	Rat	Oral	300	NOAEL	Developmental toxicity, Not Teratogenic
Embryo/Fetal Development	Rabbit	Oral	1500	NOAEL	Not Teratogenic, Maternal Toxicity
Peri/Post-natal Development	Rat	Oral	500	NOAEL	Negative

Study 2:

Pregnant Women: Based on animal data, gabapentin may cause fetal harm (see TOXICOLOGY–Reproduction Studies). In non-clinical studies in mice, rats and rabbits, gabapentin was developmentally toxic (e.g., increased fetal skeletal and visceral abnormalities, and increased embryofetal mortality) when administered to pregnant animals at doses lower than the maximum recommended human dose (MRHD) of 3600 mg/day on a body surface area (mg/m2) basis.

Teratogenic Potential: Gabapentin crosses the human placental barrier. Although there are no adequate and well-controlled studies in pregnant women, congenital malformations and adverse pregnancy outcomes have been reported with gabapentin use, both from literature and Pregnancy Registries. Since the potential risk for humans is uncertain, gabapentin should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the fetus. If women decide to become pregnant while taking GD-gabapentin, the use of this product should be carefully re-evaluated.

Study 3:

In a fertility and general reproduction study in rats with dietary doses of gabapentin up to 2000 mg/kg, (approximately 5 times the maximum daily human dose , on a mg/m2 basis), no adverse effects were noted on fertility, precoital interval, pregnancy rate, gestation length, parturition, nesting/

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	nursing behaviour, or lactation. Gabapentin did not increase the incidence of malformations, compared to controls, in the offsprings of mice, rats, or rabbits at doses up to 50, 30, and 25 times, respectively, the daily human dose of 3600 mg, (4, 5 or 8 times, respectively, the human daily dose, on mg/m^2 basis). When pregnant mice received oral doses of gabapentin (500, 1000, or 3000 mg/kg/day) during the period of organogenesis, embryofetal toxicity (increased incidences of skeletal variations) was observed at 1000 and 3000 mg/kg/day (17 and 50 times, respectively the human daily dose of 3600 mg; 1.3 and 4 times, respectively, the human daily dose on mg/m^2 basis). The noeffect dose for embryofetal developmental toxicity in mice was observed at 500 mg/kg/day (8 times the human daily dose of 3600 mg; 0.7 times the human daily dose, on mg/m^2) basis. In studies in which rats received oral doses of gabapentin (500 to 2000 mg/kg/day) during pregnancy, adverse effect on offspring development (increased incidences of hydroureter and/or hydronephrosis) were observed at all doses. The lowest dose tested is similar to the MRHD on mg/m^2 basis. When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryofetal mortality was observed at all doses tested (60, 300, or 1500 mg/kg.). The lowest dose tested is less than the MRHD on mg/m^2 basis. In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown in vitro to interfere with activity of the α2δ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.
Highly Sensitizing Potential	**Serious Dermatological Reactions:** There have been post-marketing reports of Stevens-Johnson syndrome (SJS) and Erythema multiforme (EM) in patients during treatment with gabapentin., if symptoms persists, gabapentin should be discontinued immediately

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 Epilepsy:** **Initial dose:** 300 mg orally on day one, 300 mg orally 2 times day on day two, then 300 mg orally 3 times a day on day three **Maintenance dose:** 300 to 600 mg orally 3 times a day **Maximum dose:** 3600 mg orally daily (in 3 divided doses) -Maximum time between doses in the 3 times a day schedule should not exceed 12 hours **Adverse effects:** The most common side effects of gabapentin include dizziness, fatigue, drowsiness, ataxia, peripheral edema (swelling of extremities), nystagmus and tremor. Gabapentin may also produce sexual dysfunction in some patients, symptoms of which may include loss of libido, inability to reach orgasm, and erectile dysfunction. Gabapentin should be used

	carefully in people with kidney problems due to possible accumulation and toxicity.

NOAEL/LOAEL	250 mg/kg/day

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)	1	52 weeks duration 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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg) F1 x F2 x F3 x F4 x F5 = 250 (NOAEL) x 50 5 x 10 x 1 x 1 x 5 = 50 mg/day

5. REFERENCES:

- https://www.pfizer.com/files/products/material_safety_data/PZ01158.pdf
- https://www.drugs.com/dosage/gabapentin.html
- https://en.wikipedia.org/wiki/Gabapentin