PERMITTED DAILY EXPOSURE (PDE) & OCCUPATIONAL EXPOSURE LIMIT (OEL) DETERMINATION STRATEGY FOR LACOSAMIDE (ORAL)

CONTENTS

1. BASIC INFORMATION

Toxicological Profile, Hazards Identification, Risk Assessment, Permitted Daily Exposure (PDE) and Occupational Exposure Limit (OEL) Monograph of Lacosamide	
Sponsor	Indivirtus Healthcare Services Pvt. Ltd. 522, Top Floor, Taj Plaza, TDI city, sector 118 Mohali – 160059 9131925456, 9814188308
PDE value (Oral)	1.25 mg/day or 1250 µg/day
OEL value	0.125 mg/m^3/day or 125 µg/m^3/day
Expert name	
Signature and date	
Reviewed by	
Signature and date	
Chemical name (IUPAC name)	(2R)-2-acetamido-N-benzyl-3-methoxypropanamide
Drug Product	Lacosamide

2. HAZARDS IDENTIFIED

Toxicity	Yes	No	Unknown
Genotoxicant		✓	
Carcinogen		✓	
Reproductive/developmental toxicant		✓	
Highly sensitizing potential			✓

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

Permitted daily exposure (PDE) value	**1.25 mg/day or 1250 µg/day**
Occupational exposure limit (OEL) value	**0.125 mg/m^3/day or 125 µg/m^3/day**

HAZARD IDENTIFICATION	
Pharmacodynamics data	Lacosamide enhances the slow inactivation of voltage-gated sodium channels without affecting the fast inactivation of voltage-gated sodium channels. This inactivation prevents the channel from opening, helping end the action potential.
Acute toxicity	Acute toxicity studies of lacosamide have been conducted in mice and rats. The LD_{50} value (mg/kg) ranges from 178-383 in mice and 100-253 in rats. CNS related effects were reported at high doses and primarily due to the pharmacodynamic effects of the drug.
Repeated dose toxicity	Long term toxicity studies have been conducted in mice, rats and dogs. Lacosamide caused convulsions in mice, rats and dogs and the convulsions usually occurred in the context of other significant clinical signs including one or more of tremors, ataxia, hypoactivity and recumbency, which also occurred at dose levels not associated with convulsions and mild reversible liver changes were also reported in rats.
Carcinogenicity	There was no evidence of drug related carcinogenicity in mice or rats at the doses up to 180 mg/kg/day.
Genotoxicity	Lacosamide was negative in an *in vitro* Ames test and an *in vivo* mouse micronucleus assay and an *in vivo* unscheduled DNA synthesis (UDS) test. Lacosamide induced a positive response in the *in vitro* mammalian cells at excessively high concentrations.
Reproductive/Developmental toxicity	In reproductive and developmental toxicity studies in rats and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to clinically relevant plasma exposure levels.

Highly sensitizing potential	Data regarding the sensitizing potential of lacosamide is not available in the published literature.

IDENTIFICATION OF CRITICAL EFFECTS	
Sensitive indicator of an adverse effect seen in non – clinical toxicity data	CNS toxicity (tremors, convulsions, ataxia, and hypoactivity) was reported in animal species and considered secondary to the pharmacological activity of the drug.
Clinical therapeutic and adverse effects	Lacosamide is an anticonvulsant that is used together with other medications to treat partial-onset seizures. Common adverse effects associated with lacosamide are dizziness, shakiness and unsteady walk, unusual drowsiness and trembling or shaking of the hands and feet.
Therapeutic Dose	**Initial dose:** 100 mg orally twice a day or 200 mg/day. -Titrate in increments of 100 mg (50 mg twice a day) no more frequently than once a week based on clinical response and tolerability. **Maintenance dose:** 150 to 200 mg orally twice a day or 300-400 mg/day.
NOAEL/LOAEL	NOAEL dose of 10 mg/kg/day from 12-month's toxicity study of dogs for PDE and OEL calculation.

APPLICATION OF ADJUSTMENT FACTORS – PDE AND OEL CALCULATION		
F1: Extrapolation between species	2	For the selection of toxicity study of dogs.
F2: Interindividual variability	10	Conventionally used to allow for differences between individual in the human population.
F3: Duration of exposure	10	Selection of short term (12-months) toxicity study in dogs.
F4: Nature of toxicity	2	Based on the observed pre-clinical findings.
F5: NOAEL Vs LOAEL/ Quality of data	1	Selection of NOAEL dose.
BV (The volume of air inhaled during an eight-hour work shift)	10	A healthy adult human can inhale 10 m^3 of air during an eight-hour time.
PK CORRECTION (α)	**PDE:** No factor is required. **OEL:** A factor 1 is applied.	

4. IDENTIFICATION OF THE ACTIVE SUBSTANCE

Lacosamide is a functionalized amino acid compound specifically synthesized as an anticonvulsive drug to use as add-on therapy for partial-onset seizures with antinociceptive and neuroprotective activities.

IUPAC Name: (2*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide.

Chemical Abstract services (CAS) Registry Number: 175481-36-4

Chemical description and physical properties: Lacosamide is a white to off-white crystalline powder. It is freely soluble in dimethyl sulfoxide and in ethanol. The melting point of lacosamide is about 145°C.

Molecular weight: 250.29 g/mol

Chemical formula: $C_{13}H_{18}N_2O_3$

Molecular structure:

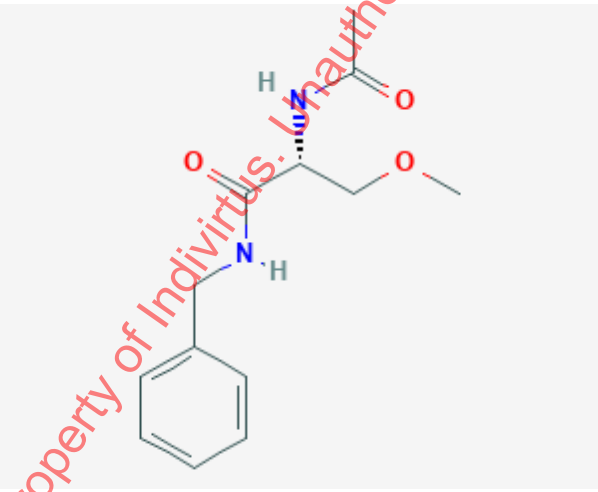

Figure 1: Structure of Lacosamide **(1).**

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 is used to determine the risk of the active pharmaceutical substance. For determination of PDE/OEL 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, a summary of pharmacological, pharmacokinetics and toxicity data of lacosamide has been presented based on the published data. The data were extracted from pub chem, drug bank, product monographs and FDA pharmacological reviews.

6. INTRODUCTION

Lacosamide is an amino acid derivative with a unique anticonvulsant activity that is used in combination with other agents as therapy of partial onset seizures.

Pharmacotherapeutic group: Antiepileptics, other antiepileptics; **ATC Code:** N03AX18 **(1).**

7. HAZARD IDENTIFICATION

a. Pharmacodynamics data

Lacosamide enhances the slow inactivation of voltage-gated sodium channels without affecting the fast inactivation of voltage-gated sodium channels. This inactivation prevents the channel from opening, helping end the action potential **(3, 4).**

b. Acute toxicity studies

Acute toxicity studies for lacosamide are shown in the following table **(4, 5, 6).**

Species	Route	Dose (mg/kg/day)	LD_{50} (mg/kg)	Key findings
Mice	Oral (p.o.)	31.6, 100, 316 & 464	383	Reduced motility, ataxia, abdominal/ lateral position, loss of righting reflex, reduced muscle tone, hind limb weakness, tremor, dyspnoea and convulsions at high doses (exaggerated pharmacological effect).
	Intravenous (I.V.)	10, 31.6, 100 & 316	178	
Rats	p.o.	31.6, 100, 316 & 464	253	
	I.V.	25, 50 & 100	>100	

c. Repeated dose toxicity studies

Repeated dose toxicity studies for lacosamide are shown in the following table **(5, 6).**

Long term toxicity study in Mice	
Species/Strain: CD-1 **Dose:** 0, 30, 60, 120 & 180 mg/kg/day **Route:** Oral (p.o.) **Duration:** 13-weeks	**Key findings: i.** Ataxia, abdominal position and reduced mortality was reported at the dose of 120 and 180 mg/kg/day. **ii.** No treatment related macroscopic or histological changes were reported. **The NOAEL (no-observed adverse-effect-level) was reported to be 60 mg/kg/day.**
Long term study in Rats	
Species/Strain: Sprague Dawley **Dose:** 0, 12.5, 25 & 50 mg/kg/day **Route:** Intravenous (I.V.) **Duration:** 14-days (2-weeks)	**Key findings: i.** Treatment related acute neurotoxicity (ataxia and tremors) were reported. **ii.** Increased in red blood cells (RBC) parameters, enzyme activities (SGOT, SGPT, ALK phos) was reported at the mid and high dose groups. **iii.** No histopathological changes were reported.
Species/Strain: Sprague Dawley **Dose:** 0, 30, 100 & 300 mg/kg/day **Route:** Oral (p.o.) **Duration:** 13-weeks	**Key findings: i.** Two treatment related deaths were reported at the high dose (300 mg/kg/day). **ii.** Muscle flaccidity, decreased motor activity, impaired righting reflex, splayed limbs, ataxia and head bobbing was reported at the dose of ≥ 200 mg/kg/day.

	iii. Loss of righting reflex, bradypnea and excessive salivation was observed at the 300 mg/kg/day dose group. **iv.** No treatment related macroscopic or histological changes were reported. **NOAEL was reported to be 100 mg/kg/day based on the clinical signs.**
Species/Strain: Sprague Dawley **Dose:** 0, 30, 90 & 180 mg/kg/day **Route:** Oral (p.o.) **Duration:** 6-months	**Key findings: i.** Excessive salivation, reduced motility, increased muscle tone, abdominal or lateral position and apathy was reported in the high dose group (180 mg/kg/day). **ii.** Increased ALT levels and liver weights were reported at the dose of 180 mg/kg/day (but the effects are reversible). **iii.** No drug related gross or histological changes were reported. **NOAEL was reported to be 90 mg/kg/day, based on the clinical signs.**
Long term study in dogs	
Species/Strain: Beagle **Dose:** 0, 4, 8 & 16 mg/kg/day **Route:** Intravenous (I.V.) **Duration:** 14-days (2-weeks)	**Key findings: i.** Clinical signs of acute neurotoxicity such as tremors, hind limb weakness, ataxia, lethargy, seizures, incoordination was reported at the high dose. **ii.** ECG (electrocardiogram) and diuretic effects were reported at the high dose.
Species/Strain: Beagle **Dose:** 0, 5, 10, 20/25mg/kg/day (high dose was adjusted from 20 to 25 mg/kg/day in week 6 because 20 mg/kg/day produce mild systemic toxicity). **Route:** Oral (p.o.) **Duration:** 12-months	**Key findings: i.** Tonic-clonic convulsions were the primarily treatment related toxicity was reported at the high dose (25 mg/kg/day). **ii.** Other drug related signs such as ataxia, tremors, reduced mortality and increased salivation was reported at the 25 mg/kg/day dose. **iii.** Treatment related effects on the peripheral arterial blood pressure was reported in both males and females. **NOAEL was reported to be 10 mg/kg/day based on the lack of toxicological findings.**

*__SGOT:__ serum glutamic-oxaloacetic transaminase; __SGPT:__ serum glutamic-pyruvic transaminase; __Alk phosp:__ Alkaline phosphatase; __ALT:__ alanine transaminase.

d. Carcinogenicity

Carcinogenicity studies for lacosamide are shown in the following table **(5, 6).**

Carcinogenic study in mice	
Species/Strain: CD-1 **Dose:** 0, 20, 60 & 180 mg/kg/day **Route:** Oral (p.o.) **Duration:**104-weeks	**Key findings:** No increase in tumour incidence in any dose group (negative carcinogenic potential).
Carcinogenic study in rats	
Species/Strain: Sprague-Dawley **Dose: Males (M):** 0, 40, 80, & 160 mg/kg/day. **Females (F):** 0, 40, 80 &160/180/200 mg/kg/day. **Route:** Oral (p.o.) **Duration:** 104-weeks	**Key findings:** No increase in tumour incidence in any dose group (negative carcinogenic potential).

e. *In-vivo/In-vitro* genotoxicity studies

In-vivo/In-vitro genotoxicity studies for lacosamide are shown in the following table **(5, 6).**

S.no.	Test Type	Dose	Result
1.	Bacterial reverse mutation assay (*Salmonella typhimurium and Escherichia coli strains)*	100-5000 µg/plate	Negative mutagenic potential
2.	*In-vitro* mammalian cell gene mutation test	500-4000 µg/mL (-) 1000-5000 µg/mL (+)	Positive potential (at high concentrations).
3.	*In-vivo* mouse micronucleus test	0, 50, 100 & 200 mg/kg	Negative genotoxic potential
4.	Unscheduled DNA synthesis (rat hepatocytes) test	125, 200, 320 & 500 mg/kg	Negative genotoxic potential

f. Reproductive and developmental studies

Reproductive and developmental toxicity for lacosamide are shown in the following table **(5, 6).**

Combined fertility and developmental study in rats	
Species/Strain: Sprague-Dawley **Dose:** 0, 25, 70 & 200 mg/kg/day	**Key findings: i.** Transient reduction in the parental body weight gain at the high dose but produced no

Combined fertility and developmental study in rats	
Route: Oral (p.o.) **Duration: M:** Before cohabitation and continuing through the day before sacrifice. **F:** 15 days before cohabitation and continuing through gestation day 17.	apparent adverse effects on the mating and fertility and litter parameters.
Embryofoetal toxicity study in rabbits (Segment-II study)	
Species/Strain: New Zealand **Dose:** 0, 6.25, 12.5 & 25 mg/kg/day **Route:** Oral (p.o.) **Duration:** Gestation day 6 to gestation day 18.	**Key findings: i.** No apparent adverse effects on the litter parameters. **ii.** Body weight gain was only slightly and transiently decreased early during the treatment period in the high dose group (25 mg/kg/day). **ii.** The increased resorption was observed at the dose of 25 mg/kg/day.
Perinatal/Postnatal toxicity study in rats (Segment-III) study	
Species/Strain: Sprague Dawley **Dose:** 0, 25, 70 & 200 mg/kg/day **Route:** Oral (p.o.) **Duration:** Gestation day 7 to lactation day 20 (PND 20).	**Key findings: i.** Increased number of still born pups was reported at all doses. **ii.** Pup body weight were decreased at the high dose group. **iii.** Decreased viability index was reported at the high dose (200 mg/kg/day).

***There are no adequate data on the developmental risks associated with the use of lacosamide in pregnant women.*

g. Highly sensitizing potential

No relevant preclinical and clinical data regarding the sensitization potential was available in literature.

8. IDENTIFICATION OF CRITICAL EFFECTS

Scientific evaluation of published pharmacological and toxicological data including clinical and non-clinical reports helps 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.

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

CNS toxicity (tremors, convulsions, ataxia, hypoactivity) was reported in animal species and considered secondary to the pharmacological activity of the drug.

b. Clinical therapeutic and adverse effects

Lacosamide is an anticonvulsant that is used together with other medications to treat partial-onset seizures **(7).**

Indication	Dosage
Usual Adult dose for epilepsy	**Initial dose:** 100 mg orally twice a day or 200 mg/day. -Titrate in increments of 100 mg (50 mg twice a day) no more frequently than once a week based on clinical response and tolerability. **Maintenance dose:** 150 to 200 mg orally twice a day or 300-400 mg/day.

Adverse effects:

Common adverse effects associated with lacosamide are dizziness, shakiness and unsteady walk, unusual drowsiness and trembling or shaking of the hands and feet **(7).**

In controlled adjunctive therapy clinical trials in patients with partial-onset seizures, 924 patients received lacosamide tablets. In the controlled monotherapy clinical trial in patients with partial onset seizures, 444 patients received at least one dose of lacosamide tablets. Some of the most frequently reported adverse reactions in controlled clinical trials with lacosamide treatment were dizziness, headache, nausea, and vision-related events (e.g., diplopia, blurred vision). They were dose-related and usually mild to moderate in intensity **(4).**

9. RATIONALE FOR NO/LOWEST OBSERVED ADVERSE EFFECT LEVEL (NOAEL/LOAEL) VALUE SELECTION

The toxicity studies of lacosamide have been conducted in rodents and non-rodents over the period of 12-months. NOAEL value of 10 mg/kg/day is selected from the 12-months oral toxicity study in dogs, because dogs are supposed to be relevant to human species and study of longer duration is preferred for the calculation of the PDE and OEL value.

10. APPLICATION OF ADJUSTMENT FACTORS (RATIONALE FOR THE ADJUSTMENT FACTORS)

A series of modifying or safety factors are used when NOAEL/LOAEL is based on studies of different types and duration in different species to provide a risk assessment for human exposure **(8, 9).**

a. F1: Interspecies difference

This factor takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area is calculated as S= KM 0.67where 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 based on the selection of toxicity study of dogs.

b. F2: Inter-individual differences

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

c. F3: Duration of exposure

A variable factor up to 10 is used for the duration of the 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. 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 used because of selection of short term (12-months) toxicity 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. 1 for the embryo or fetal toxicity or mortality associated with maternal toxicity; 5 for the 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 2 is used based on the pre-clinical findings.

e. F5: NOAEL vs LOAEL/quality of data

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

f. PK CORRECTION (α)

A variable factor is applied because PDE value derived for an active substance (contaminant) generally is based on studies applying the intended clinical route of administration, a different route of administration may be applied for the active substance or medicinal product subsequently produced in the shared facility. Changing the route of administration may change the bioavailability; hence correction factors for route-to-route extrapolation should be applied if there are clear differences in route specific bioavailability. As bioavailability may vary between species, the correction factors for route-to-route extrapolation should preferably be based on human data or in the case of veterinary medicinal products, data in the relevant target animal.

PDE: No pharmacokinetic correction is applied for the PDE calculation, since the same route of the administration is used.

OEL: For OEL calculation, a factor of 1 (Inhalational/Oral bioavailability ratio) is used, because the absolute bioavailability of lacosamide is 100% **(3).**

g. BV

It is volume of air inhaled during an eight-hour work shift or when the worker exposure is measured, it is calculated what concentration it would be if the exposure was constant over 8 hours – called the 8-hour Time Weighted Average, or daily exposure. A healthy adult human can inhale **10 m^3** of air during an eight-hour time. Thus, a factor of 10 is used for OEL calculation.

PDE CALCULATION

The PDE calculation is generally presented in the format **(8, 9).**

$$\text{PDE (mg/day)} = \frac{\text{NOAEL (mg/kg/day) x weight adjustment (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$$

$$= \frac{10 \text{ x } 50}{2 \text{ x } 10 \text{ x } 10 \text{ x } 2 \text{ x } 1}$$

$$= 1.25 \text{ mg/day}$$

Hence, the PDE value of lacosamide is 1.25 mg/day or 1250 µg/day.

OEL CALCULATION

OEL can be calculated by using the formula **(10).**

$$\text{OEL } (mg/m^3/day) = \frac{\text{NOAEL (mg/kg/day) X Weight adjustment (kg)}}{\text{F1 x F2 x F3 x F4 x F5 x } \alpha \text{ x BV}}$$

$$= \frac{10 \text{ x } 50}{2 \text{ x } 10 \text{ x } 10 \text{ x } 2 \text{ x } 1 \text{ x } 1 \text{ x } 10}$$

$$= 0.125 \text{ mg/m}^3\text{/day}$$

Hence, the OEL value of lacosamide is 0.125 mg/m^3/day or 125 µg/m^3/day.

11. REFERENCES

1. **Lacosamide, PubChem.** https://pubchem.ncbi.nlm.nih.gov/compound/Lacosamide
2. **Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities EMA/CHMP/ CVMP/ SWP/169430/2012., 2014.** https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-setting-health-based-exposure-limits-use-risk-identification-manufacture-different_en.pdf.
3. **Lacosamide, Drug Bank.** https://www.drugbank.ca/drugs/DB06218
4. **Lacosamide, Product Monograph, 2018.** https://www.sandoz.ca/sites/www.sandoz.ca/files/9932-Sandoz%20Lacosamide%20Product%20Monograph.pdf
5. **Lacosamide, FDA pharmacological review, 2008.** https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022253s000_022254s000_PharmR_P1.pdf
6. **Lacosamide, FDA Pharmacological review, 2008.** https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022253s000_022254s000_PharmR_P3.pdf
7. **Lacosamide, Drugs.com.** https://www.drugs.com/dosage/lacosamide.html
8. **ICH guideline Q3D (R1) on elemental impurities, EMA/CHMP/ICH/353369/2013, Committee for Human Medicinal Products, 28 March 2019.** https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-32.pdf
9. **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.** https://www.ema.europa.eu/en/documents/scientific-guideline/draft-vich-gl-18-residual-solvents-new-veterinary-medicinal-products-active-substances-excipients_en.pdf
10. **Lovsin Barle, E., Winkler, G.C., Glowienke, S., Elhajouji, A., Nunic, J. and Martus, H.J., 2016. Setting occupational exposure limits for genotoxic substances in the pharmaceutical industry. Toxicological Sciences, 151(1), pp.2-9.** https://pubmed.ncbi.nlm.nih.gov/27207978/

ANNEXURE I: PHARMACOKINETICS

Absorption: Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%.

Distribution: The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Metabolism: The metabolism of lacosamide has not been completely characterized. Approximately 95% of the dose is excreted in the urine as drug and metabolites. The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite, which has no known pharmacological activity (less than 30%).

Excretion: Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of 100 mg radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours and is not altered by different doses, multiple dosing or intravenous administration.

ANNEXURE II: GLOSSARY

ADI/ADE: Acceptable daily intake/ Acceptable daily exposure

AUC: Area under the curve

GRAS: Generally regarded as safe

GLP: Good laboratory practice

GMP: Good manufacturing practice

LD: Lethal dose

LD_{LO}: Lethal Dose Low

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, taking into account 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 analyzed using computer modeling 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.

Material safety data sheet (MSDS): compilation of information required under the U.S. OSHA Hazard Communication Standard on the identity of hazardous substances, health and physical hazards, exposure limits, and precautions.

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.

ANNEXURE III: SUMMARY OF THE EXPERT CV