PERMITTED DAILY EXPOSURE FOR LEVOSULPIRIDE

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 Levosulpiride 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:

Levosulpiride is a substituted benzamide antipsychotic reported to be a selective antagonist of dopamine D2 receptor activity on both central and peripheral levels. It is an atypical neuroleptic and a prokinetic agent. Levosulpiride is also claimed to have mood elevating properties.

Side effects include amenorrhea, gynecomastia, galactorrhea, changes in libido, and neuroleptic malignant syndrome. A case of rapid onset resistant dystonia caused by low dose levosulpiride was reported in India.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

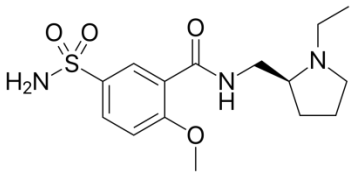
IUPAC name: N-[[(2S)-(−)-1-Ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-sulfamoylbenzamide

Chemical Abstract Services (CAS) Registry Number: 23672-07-3

Molecular Weight: 341.43 g·mol−1

Chemical Formula: $C_{15}H_{23}N_3O_4S$

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

Levosulpiride is a substituted benzamide derivative and a selective dopamine D_2 antagonist with antipsychotic and antidepressant activity. Other benzamide derivatives include metoclopramide, tiapride, and sultopride.

Pharmacokinetics data

Levosulpiride exhibited linear pharmacokinetic properties over the dose range of 25 to 100 mg by PO route and 25 to 75 mg by IM route. The corresponding mean AUC_{0-t} increased from 449 to 1443 ng/h/mL and from 2874 to 7559 ng/h/mL, respectively. After repeated PO and IM administration, steady state was reached on day 4 of multiple dosing with accumulation index of 1.8 and on day 2 of multiple dosing with accumulation index of 1.3, respectively. The bioavailability of Levosulpiride via IM and PO routes was 96.8% and 23.4%, respectively. No significant differences were observed on PK properties between male and female subjects. More than half (23 of 42 [54.8%]) of healthy volunteers experienced one or more adverse events in total, including constipation, diarrhea, drowsiness, skin rash, and extrapyramidal reactions.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Rat	LD50	Oral	2600	Null	Drugs of the Future., 12(944), 1987
Rat	LD50	Intraperitoneal	270	Null	Drugs of the Future., 12(944), 1987
Rat	LD50	Intravenous	53	Null	Drugs of the Future., 12(944), 1987
Mouse	LD50	Oral	2450	Null	Drugs of the Future., 12(944), 1987
Mouse	LD50	Intraperitoneal	170	Null	European Journal of Medicinal Chemistry--Chimie Therapeutique., 17(437), 1982
Rabbit	LD50	Oral	1500	Null	Drugs of the Future., 12(944), 1987
Rabbit	LD50	Intravenous	42	Null	Drugs of the Future., 12(944), 1987

Repeated Dose Toxicity (Chronic Toxicity)

Sub-acute toxicity tests were conducted by administering the active ingredient in rat, rabbit and dog, daily, for 12-13 weeks. The appearance of any toxic symptoms was not observed at doses of:

- 25 mg/kg sc and 300 mg/kg p.o. in the rat,
- 250 mg/kg p.o. and 12.5 mg/kg i.m. in rabbits,
- 50 and 100 mg/kg p.o. in the dog.

To evidentiatethe chronic toxicity after administration of the drug for 180-190 days, the following doses were well tolerated:

- 100 mg/kg p.o. and 20 mg/kg s.c. in the rat,

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SUMMARY OF HAZARD IDENTIFICATION:	
	• 10 mg/kg i.m. in rabbits and • 20 mg/kg p.o. in the dog
Carcinogenicity	Studies performed in rats and mice, administering the medicine at a dose higher than that expected for man, have shown that Levosulpiride do not possess carcinogenic properties. Studies carried out in rats and rabbits have shown that the medicine is not teratogenic.
In vivo/In vitro Genotoxicity Studies	In vitro tests have ruled out that the medicine possesses mutagenic properties.
Reproductive/Developmental Toxicity	Evaluation of pregnancy outcomes of women who were inadvertently exposed to Levosulpiride in early pregnancy. All 162 consecutive singleton pregnant women counselled through the Korean Motherisk Program, Cheil General Hospital, between April 2001 and April 2014, on teratogenic risk after inadvertent exposure to Levosulpiride in early pregnancy were enrolled in this study. The women were exposed to Levosulpiride at median 4.8 gestational weeks. The rate of miscarriage was not significantly different between groups (9.2% in those exposed and 5.5% in the non-exposed; p = .084). The rate of major malformations was not significantly different between exposed (2.7%) and non-exposed pregnancies (4.4%) (p = .481). All other pregnancy outcomes between the two groups were comparable (p > .05). Our data suggest that levosulpiride causes no significant adverse effects on pregnancy outcomes and therefore may be not a major teratogen.
Highly Sensitizing Potential	Levosulpiride may cause skin rashes.

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	**Clinical Therapeutic Dose:** Initial Dose: 400 mg twice daily Maximum daily dose: 1200 mg twice daily. **Adverse Effects:** Side effects include amenorrhea, gynecomastia, galactorrhea, changes in libido, and neuroleptic malignant syndrome.

NOAEL/LOAEL	0.5 mg/kg/day NOAEL value for minimum therapeutic dose.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	Minimum human dose selected.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	2	6 months 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	

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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 = 0.5 (NOAEL) x 50 1 x 10 x 2 x 1 x 5 = 0.25 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Levosulpiride
- http://mri.cts-mrp.eu/download/IT_H_0367_001_FinalSPC.pdf
- https://www.medicines.org.uk/emc/product/2430/smpc
- https://www.researchgate.net/publication/317701246_Pregnancy_outcomes_in_women_reporting_ingestion_of_levosulpiride_in_early_pregnancy