PERMITTED DAILY EXPOSURE FOR AMISULPRIDE

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 Amisulpride 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:

Amisulpride is an antiemetic and antipsychotic medication used at lower doses intravenously to prevent and treat postoperative nausea and vomiting; and at higher doses orally and intramuscularly to treat schizophrenia and acute psychotic episodes. It is also used to treat dysthymia.

It is usually classed with the atypical antipsychotics. Chemically it is a benzamide and like other benzamide antipsychotics, such as sulpiride, it is associated with a high risk of elevating blood levels of the lactation hormone, prolactin (thereby potentially causing the absence of the menstrual cycle, breast enlargement, even in males, breast milk secretion not related to breastfeeding, impaired fertility, impotence, breast pain, etc.), and a low risk, relative to the typical antipsychotics, of causing movement disorders. It has also been found to be modestly more effective in treating schizophrenia than the typical antipsychotics.

Amisulpride is believed to work by blocking, or antagonizing, the dopamine D2 receptor, reducing its signalling. The effectiveness of Amisulpride in treating dysthymia and the negative symptoms of schizophrenia is believed to stem from its blockade of the presynaptic dopamine D2 receptors. These presynaptic receptors regulate the release of dopamine into the synapse, so by blocking them Amisulpride increases dopamine concentrations in the synapse. This increased dopamine concentration is theorized to act on dopamine D1 receptors to relieve depressive symptoms (in dysthymia) and the negative symptoms of schizophrenia.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Amisulpride is an antiemetic and antipsychotic medication used at lower doses intravenously to prevent and treat postoperative nausea and vomiting; and at higher doses orally and intramuscularly to treat schizophrenia and acute psychotic episodes.

IUPAC NAME: 4-amino-N-[(1-ethylpyrrolidin-2-yl) methyl]-5-ethylsulfonyl-2-methoxybenzamide

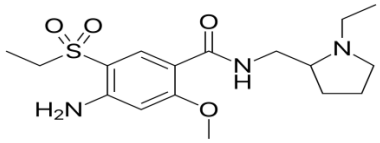
Chemical Abstract Services (CAS) Registry Number: 71675-85-9

Molecular Weight: 369.48 g/mol

Chemical Formula: $C_{17}H_{27}N_3O_4S$

Chemical Description & Physical Properties:

Molecular Structure:



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4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Amisulpride binds selectively to the human dopaminergic D2 (Ki 2.8 nM) and D3 (Ki 3.2 nM) receptor subtypes without any affinity for D1, D4 and D5 receptor subtypes (Ki > 1M). Unlike classical and atypical neuroleptics, Amisulpride displays low affinity for serotonin, adrenergic, histamine receptor subtypes, muscarinic receptors and sigma sites. In the rodent, it preferentially blocks post-synaptic D2 receptors located in the limbic structures as compared to those in the striatum as indicated by its reversal of d-amphetamine-induced hyperactivity without affecting stereotypies. In addition, it does not induce catalepsy and it does not produce D2 hypersensitivity after repeated treatment. Moreover, it preferentially blocks pre-synaptic D2/D3 dopamine receptors, producing dopamine release responsible for its disinhibitory effects. This atypical pharmacological profile may explain Amisulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade located in the limbic areas and its efficacy against negative symptoms, at lower doses, through presynaptic dopamine receptor blockade. In addition, the reduced tendency of Amisulpride to produce extrapyramidal side effects may be related to its preferential limbic activity.
Acute Toxicity	<table><tr><th>Organism</th><th>Test Type</th><th>Route</th><th>Dose (mg/kg)</th></tr><tr><td rowspan="4">Mouse</td><td rowspan="4">LD50</td><td>Oral</td><td>1024</td></tr><tr><td>Intraperitoneal</td><td>175</td></tr><tr><td>Subcutaneous</td><td>224</td></tr><tr><td>Intravenous</td><td>56</td></tr></table> Overdoses of Amisulpride have been linked with Torsades de pointes.
Repeated Dose Toxicity (Chronic Toxicity)	Amisulpride is administered orally twice daily. The recommended dosages of Amisulpride are 50 to 300 mg/day for the treatment of patients with predominantly negative symptoms of Schizophrenia and 400 to 800 mg/day for those with positive symptoms. Dosages as high as 1200 mg/day have been studied.

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SUMMARY OF HAZARD IDENTIFICATION:	
Carcinogenicity	In carcinogenicity studies, Amisulpride was administered in the diet of mice and rats for up to two years. Treatment of mice was associated with increases in malignant mammary gland tumors and pituitary adenomas in females at all dose levels, but there was no tumorigenic response in males (doses were equivalent to 0.1, 0.2 and 0.5 times the maximum human dose of 1200 mg/day on a body surface area basis). Treatment of rats resulted in increased incidences of malignant mammary gland tumors in both sexes, malignant pituitary tumors and adrenal medullary phaeochromocytomas in males, and malignant pancreatic islet cell tumors in both sexes, at doses achieving lower systemic drug exposure (plasma AUC) than in humans at the maximal recommended dose. Increases in mammary gland, pituitary, adrenal and pancreatic endocrine tumors in rodents have been reported for other antipsychotic medicines, and are considered to result from increased prolactin secretion. The relevance of prolactin-mediated endocrine tumors in rodents for human risk is unknown. In clinical trials, Amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic medicines and mammary tumourigenesis. However, since tissue culture experiments indicate that about one-third of human breast cancers are prolactin-dependent in vitro, Amisulpride should be used cautiously in patients with previously-detected breast cancer or in patients with pituitary tumors.
In vivo/In vitro Genotoxicity Studies	Amisulpride showed no Genotoxicity in in vitro tests for bacterial gene mutation, or in in vitro and in vivo tests for clastogenic activity.
Reproductive/Developmental Toxicity	Reproductive studies performed in the rat, rabbit and mouse did not show any Teratogenic potential
Highly Sensitizing Potential	No any sensitivity observed

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No severe toxicity was observed
Clinical therapeutic and adverse effects	**Psychiatric disorders:** Insomnia, Anxiety, Agitation & Orgasmic dysfunction. **Nervous system disorders:** Extrapyramidal symptoms may occur: Tremor, Rigidity, Hypokinesia, Hypersalivation, Akathisia, Dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of Amisulpride upon administration of Antiparkinsonian medication, Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence. **Eye disorders:** Common: blurred vision (see Section Driving a vehicle or performing other hazardous tasks) **Cardiac disorders:** Common: QT interval prolongation (see Section Warnings)

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	Vascular disorders: Common: hypotension **OVERDOSAGE:** Drowsiness, Sedation, Hypotension, Extrapyramidal symptoms and Coma. **Therapeutic Dose Adults:** 50 mg/day (1 mg/kg/day)

NOAEL/LOAEL	Amisulpride at 200 mg/day (the highest oral dose evaluated) was assessed to be the No Observed Adverse Effects Level (NOAEL).

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)	10	Short 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
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{200 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 4 mg/day

5. REFERENCES:

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5. https://pubchem.ncbi.nlm.nih.gov/compound/Amisulpride#section=GHS-Classification.

6. https://www.ecnp.eu/presentationpdfs/71/P.3.c.005.pdf.

7. https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/no-observed-adverse-effect-level.