PERMITTED DAILY EXPOSURE FOR ALPRAZOLAM

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 **Alprazolam** 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:

Alprazolam is a short-acting benzodiazepine. It is most commonly used in short term management of anxiety disorders, specifically panic disorder or generalized anxiety disorder (GAD). Other uses include the treatment of chemotherapy-induced nausea, together with other treatments. GAD improvement occurs generally within a week. Alprazolam is generally taken by mouth.

Common side effects include sleepiness, depression, headaches, feeling tired, dry mouth, and memory problems. Other rare risks include suicide, possibly due to loss of inhibition. Gradually decreasing the dose over weeks or months may be required. Alprazolam, like other benzodiazepines, acts through the GABAA receptor.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

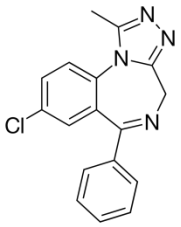
IUPAC NAME: 8-Chloro-1-methyl-6-phenyl-4H-[1, 2, 4] triazolo [4,3-a] [1,4]benzodiazepine.

Chemical Abstract Services (CAS) Registry Number: 28981-97-7

Molecular Weight: 308.77 g·mol−1

Chemical Formula: $C_{17}H_{13}ClN_4$

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

Alprazolam is indicated to treat anxiety and panic disorders. The mechanism by which its cell receptor interactions translate to a clinical effect is not known. Alprazolam exerts its effects through interaction with BNZ-1, BNZ-2, and GABA-A receptors. Alprazolam binding to BNZ-1 is thought to influence sedation and anti-anxiety, BNZ-2 may influence memory, coordination, muscle relaxation, and anticonvulsive activity, and GABA-A may calm patients by increasing the affinity of GABA-A receptors for GABA.
The metabolism of alprazolam is mediated largely through the action of CYP3As and so alprazolam is contraindicated with CYP3A inhibitors such as Ketoconazole and Itraconazole.
Alprazolam, like other benzodiazepines, can cause dependancy and so when stopping treatment doses should be tapered down gradually. Alprazolam's adverse effects are generally related to the sedating effects of the drug. This effect has lead to abuse of alprazolam with alcohol to potentiate its sedating effect, which may lead to coma and death.

Pharmacokinetic data

Absorption: Oral bioavailability of a standard release tablet of Alprazolam is 84-91% with a time to maximum concentration of 1.8 hours. A 1mg oral dose of alprazolam leads to a maximum plasma concentration of 12-22mcg/L. Alprazolam is rapidly absorbed in the gastrointestinal tract.
Data for the area under the curve and the effect of taking Alprazolam with food are not readily available.

Volume of Distribution: Volume of distribution following oral administration is 0.8-1.3L/kg[2] Alprazolam crosses the blood-brain barrier.

Protein Binding: Alprazolam is 80% protein bound in serum. Label The majority of this protein binding is to serum albumin. Label, Alprazolam is also bound to alpha1-acid glycoprotein with low frequency.

Metabolism: Alprazolam is metabolized to less effective metabolites by various CYPs including CYP3A4, CYP3A5, CYP3A7 and CYP2C9. Label,5,6,9 The majority of alprazolam metabolism is mediated by hydroxylation via CYP3As.Label,5,6,2,9 4-hydroxyalprazolam has 20% the binding affinity of the parent drug, alpha-hydroxyalprazolam has 66% the affinity, and the benzophenone metabolite has <1% the affinity.

Route of Elimination: Alprazolam is mainly eliminated in the urine. A large portion of the dose is eliminated as unmetabolized alprazolam. <10% of the dose is eliminated as alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam.

Acute Toxicity

Species	Route	End Point	Dose (mg/g)
Rat	Oral	LD_{50}	1220
Rat	Oral	LD_{50}	3100
Mouse	Oral	LD_{50}	1410-1700
Rat	Intravenous	LD_{50}	~ 15

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Duration (Year)	Species	Route	Dose (mg/kg/day)	End Point	Target Organ
1	Dog	Oral	3-30	LOAEL	Central Nervous System
1	Rat	Oral	25	NOAEL	None Identified
2	Rat	Oral	3,10,30	Eyes	-

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Women	TDLo	Oral	0.02	Behavioral: euphoria	American Journal of Psychiatry., 141(1127), 1984
Child	TDLo	Oral	0.075	Behavioral: hallucinations, distorted perceptions; behavioral: muscle weakness	Medical Toxicology., 1(411), 1986 [PMID:3540518]
Rat	LD_{50}	Oral	1220	Behavioral: changes in motor activity (specific assay); behavioral: antipsychotic; lungs, thorax, or respiration: respiratory depression	Yakuri to Chiryo. Pharmacology and Therapeutics., 8(4695), 1980
Rat	LD_{50}	Intraperitoneal	355	Behavioral: changes in motor activity (specific assay); behavioral: antipsychotic; lungs, thorax, or respiration: respiratory depression	Yakuri to Chiryo. Pharmacology and Therapeutics., 8(4695), 1980
Rat	LD_{50}	Subcutaneous	5000	Autonomic nervous system: smooth muscle relaxant (mechanism undefined, spasmolytic); behavioral: food intake (animal); behavioral: ataxia	Yakuri to Chiryo. Pharmacology and Therapeutics., 8(4695), 1980
Mouse	LD_{50}	Oral	770	Behavioral: somnolence (general depressed activity); autonomic nervous system: smooth muscle relaxant (mechanism undefined, spasmolytic)	Cesko-Slovenska Farmacie., 37(443), 1988 [PMID:3245968]
Mouse	LD_{50}	Intraperitoneal	380	Behavioral: food intake (animal); behavioral: muscle weakness; behavioral: antipsychotic	Yakuri to Chiryo. Pharmacology and Therapeutics., 8(4687), 1980
Mouse	LD_{50}	Subcutaneous	5000	Autonomic nervous system: smooth muscle relaxant (mechanism undefined, spasmolytic); behavioral: food intake (animal)	Yakuri to Chiryo. Pharmacology and Therapeutics., 8(4687), 1980
Man	TDLo	Oral	0.16	Behavioral: excitement	American Journal of Psychiatry., 142(859), 1985 [PMID:2861755]

A retrospective study was conducted of 415 alprazolam ingestions in dogs: 238 suspected alprazolam toxicoses in dogs were evaluated. Clinical signs were

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SUMMARY OF HAZARD IDENTIFICATION:

ataxia/disorientation, depression, hyperactivity, vomiting, weakness, tremors, vocalization, tachycardia, tachypnea, hypothermia, diarrhea, and increased salivation that developed within 10-30 min post-ingestion. Other experiments in animals have indicated cardiopulmonary collapse can occur following massive intravenous doses of alprazolam.

Carcinogenicity

Duration	Species	Route	Dose (mg/kg/Day)	Effects
2 yrs.	Rat	Oral	30	Not Carcinogenic
104 weeks	Mouse	Oral	10	Not Carcinogenic

No evidence of carcinogenic potential was observed during 2 year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day and in mice at dose up to 10 mg/kg/day

In vivo/In vitro Genotoxicity Studies

Study Type	Cell Type/Organisms	Results
Bacterial Mutagenicity (Ames)	Salmonella	Negative
In vivo micronucleus	Rat	Negative
Direct DNA interaction	Salmonella	Negative

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg. Alprazolam also was not mutagenic in vitro in the DNA Damage/Alkaline Elution Assay or the Ames Assay. Alprazolam was also studied using Allium cepa test, where it induced chromosomal and cytological aberrations, especially nuclear alterations.

Reproductive/Developmental Toxicity

Study Type	Species	Route	Dose (mg/kg/day)	End Point	Effect
Reproductive & Fertility	Rat	Oral	5	NOAEL	Negative
Embryo/ Fetal Development	Rat	Oral	5	NOAEL	Embryo Toxicity
Embryo/ Fetal Development	Rabbit	Oral	0.5	NOAEL	Embryo Toxicity/ Teratogenic

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day. Altered behaviors in several mouse strains after prenatal exposure to alprazolam suggests a vulnerability of GABA-benzodiazepine receptor formation in fetal brain development. Mice offspring that were exposed prenatally to alprazolam demonstrated more individual rather than group activities, avoidance of open areas, and aggression in males.

Alprazolam is a pregnancy category D teratogen meaning there is evidence of risk to the fetus of a mother taking alprazolam but in some cases the benefit may outweigh the risk. Children born to these mothers are also at risk of withdrawal symptoms, flaccidity, and respiratory issues.

Benzodiazepines are expressed in human breast milk and so nursing is generally not recommended in mothers taking alprazolam.

Highly Sensitizing Potential

Hypersensitivity reactions including anaphylaxis are very rare (Brigby, 1986).

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.

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Clinical therapeutic and adverse effects	**Usual Adult Dose for Anxiety:** Immediate-release tablets/orally disintegrating tablets (ODT): 0.25 to 0.5 mg orally administered 3 times a day Maximum dose: 4 mg/day **Usual Adult Dose for Panic Disorder:** Immediate-release tablets/ODTs: 0.5 mg orally administered 3 times a day Maximum dose: 10 mg/day
NOAEL/LOAEL	NOAEL value for Rat is 25 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	1 year 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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{25 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 5 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Alprazolam.
- https://pfe-pfizercom-prod.s3.amazonaws.com/products/material_safety_data/Alprazolam_XR_Tablets_6-march-2019.pdf