PERMITTED DAILY EXPOSURE FOR ACETAZOLAMIDE

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 Acetazolamide 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:

Acetazolamide is a medication used to treat glaucoma, epilepsy, altitude sickness, periodic paralysis, idiopathic intracranial hypertension (raised brain pressure of unclear cause), and heart failure. It may be used long term for the treatment of open angle glaucoma and short term for acute angle closure glaucoma until surgery can be carried out. It is taken by mouth or injection into a vein. Common side effects include numbness, ringing in the ears, loss of appetite, vomiting, and sleepiness. It is not recommended in those with significant kidney problems, liver problems, or who are allergic to sulfonamides. Acetazolamide is in the diuretic and carbonic anhydrase inhibitor families of medication. It works by decreasing the amount of hydrogen ions and bicarbonate in the body.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Acetazolamide, an inhibitor of the enzyme carbonic anhydrase, is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for Acetazolamide is N-(5-Sulfamoyl-1, 3, 4-thiadiazol-2yl)-acetamide and has the following structural formula:

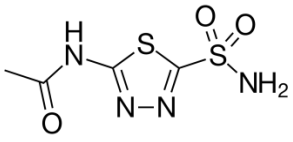
IUPAC NAME: N-(5-Sulfamoyl-1, 3, 4-thiadiazol-2-yl) acetamide.

Chemical Abstract Services (CAS) Registry Number: 216665-38-2

Molecular Weight: 222.24 g·mol−1

Chemical Formula: $C_4H_6N_4O_3S_2$

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

Acetazolamide is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion, in the treatment of certain convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention. Acetazolamide is not a mercurial diuretic. Rather, it is a non-bacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides.

Pharmacokinetic data

Absorption: Acetazolamide is fairly rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 2 hours after administration by mouth.

Distribution: It has been estimated to have a plasma half-life of about 4 hours. It is tightly bound to carbonic anhydrase and accumulates in tissues containing this enzyme, particularly red blood cells and the renal cortex. It is also bound to plasma proteins.

Elimination: It is excreted unchanged in the urine; renal clearance being enhanced in alkaline urine.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Man	TDLo	Oral	54	Lungs, thorax, or respiration: dyspnea	Archives of Internal Medicine., 143(1278), 1983
Rat	LD_{50}	Intraperitoneal	2750	Null	Nippon Yakurigaku Zasshi. Japanese Journal of Pharmacology., 56(4)(134S), 1960
Mouse	LD_{50}	Oral	4300	Null	Acta Biologica et Medica Germanica., 21(193), 1968 [PMID:4973050]
Mouse	LD_{50}	Intraperitoneal	1175	Null	Russian Pharmacology and Toxicology, 39(255), 1976
Mouse	LD_{50}	Subcutaneous	3000	Null	Drugs in Japan,6(15), 1982
Mouse	LD_{50}	Intravenous	3000	Null	Drugs in Japan, 6(15) ,1982
Dog	LD_{50}	Intravenous	2000	Null	Drugs in Japan, 6(15) ,1982
Guinea Pig	LD_{50}	Subcutaneous	1500	Null	Drugs in Japan, 6(15) ,1982

Repeated Dose Toxicity (Chronic Toxicity)

The subchronic toxicity has been evaluated in rats and dogs. It was well tolerated in rats at relatively high oral doses for 6 months. Deep respiration, vomiting, listlessness, and occasional muscular fibrillation accompanied by anorexia and lethargy was observed in dogs treated with high dosages for 16 months; all of these signs disappeared by the fifth week.

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of acetazolamide have not been conducted.

In vivo/In vitro Genotoxicity Studies

In a bacterial mutagenicity assay, acetazolamide was not mutagenic when evaluated with and without metabolic activation.

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SUMMARY OF HAZARD IDENTIFICATION:

Reproductive/Developmental Toxicity

The drug had no effect on fertility when administered in the diet to male and female rats at a daily intake of up to 4 times the recommended human dose of 1000 mg in a 50 kg individual.

Pregnancy Teratogenic Effects: Pregnancy Category C Acetazolamide administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits. There are no adequate and well-controlled studies in pregnant women. Acetazolamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Measurement	Route organism	Dose	Effect	Reference
Reproductive effects	Intraperitoneal/mouse	1500 mg/kg (9D pregnant)	Reproductive: Specific developmental abnormalities: Central nervous system	Teratology, The International Journal of Abnormal Development, 60,137,1999
Reproductive effects	Intraperitoneal/rat	1 gm/kg (10D pregnant)	Reproductive: Effects on fertility: Post- implantation mortality (e.g., dead and/or resorbed implants per total number of implants); Reproductive: Effects on embryo or fetus: Fetal death; Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 1,51,1968
Reproductive effects	Intraperitoneal/hamster	300 mg/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 4,95,1971
Reproductive effects	Intraperitoneal/hamster	600 mg/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Central nervous system	Teratology, The International Journal of Abnormal Development, 4,95,1971
Reproductive effects	Intravaginal/hamster	110 mg/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 7,209,1973
Reproductive effects	Oral/mouse	850 mg/kg (10D pregnant)	Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 28,355,1983
Reproductive effects	Subcutaneous/rat	1 gm/kg (10D pregnant)	Reproductive: Effects on embryo or fetus: Fetal death; Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 1,51,1968
Reproductive effects	Subcutaneous/mouse	1 gm/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Central nervous system; Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 10,221,1974

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SUMMARY OF HAZARD IDENTIFICATION:

	Reproductive effects	Subcutaneous/mouse	200 mg/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Craniofacial (including nose and tongue)	Teratology, The International Journal of Abnormal Development, 27,51,1983
	Reproductive effects	Subcutaneous/mouse	1 gm/kg (8D pregnant)	Reproductive: Effects on newborn: Live birth index (Litter size (e.g., # fetuses per litter; measured after birth); Reproductive: Effects on newborn: Growth statistics (e.g., reduced weight gain)	Teratology, The International Journal of Abnormal Development, 28,45,1983
	Reproductive effects	Subcutaneous/mouse	3 gm/kg (9-11D pregnant)	Reproductive: Effects on embryo or fetus: Fetal death	Teratology, The International Journal of Abnormal Development, 28,45,1983
	Reproductive effects	Subcutaneous/mouse	200 mg/kg (8D pregnant)	Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 28,45,1983
	Reproductive effects	Subcutaneous/rabbit	1500 mg/kg (13D pregnant)	Reproductive: Effects on fertility: Litter size (e.g., # fetuses per litter; measured before birth); Reproductive: Effects on embryo or fetus: Fetotoxicity (except death, e.g., stunted fetus); Reproductive: Effects on embryo or fetus: Cytological changes (including somatic cell genetic material)	Teratology, The International Journal of Abnormal Development, 15,199,1977
	Reproductive effects	Subcutaneous/rabbit	1500 mg/kg (13D pregnant)	Reproductive: Specific developmental abnormalities: Musculoskeletal system	Teratology, The International Journal of Abnormal Development, 15,199,1977

Highly Sensitizing Potential	There have been several reports of skin rash and serum sickness hypersensivity in patients on chronic therapy (Kristinsson, 1966). Acetazolamide is a sulfonamide derivative and shares the incidence of Hypersensitivity reactions (McEvoy, 1995). There are rare true allergic reactions reported to Acetazolamide.

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 Edema** Initial dose: 250 to 375 mg orally/IV once a day Maintenance dose: One dose every other day or once a day for 2 days alternating with a day of rest. **Usual Adult Dose for Acute Mountain Sickness** 500 to 1000 mg orally per day in divided doses **Usual Adult Dose for Glaucoma** Immediate-release (IR) tablets: 250 to 1000 mg orally per day; amounts over 250 mg should be administered in divided doses

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	Extended-release (ER) capsules: 500 mg orally 2 times a day **Usual Adult Dose for Seizure Prophylaxis** Initial dose: 8 to 30 mg/kg orally/IV in divided doses Range: 375 to 1000 mg per day **Adverse effects:** The more serious effects include blood disorders, skin toxicity and renal stone formation. Stevens-Johnson syndrome has not been reported (Rubenstein, 1975, as quoted by Dollery, 1991).

NOAEL/LOAEL	50 mg/kg/day	
APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2.5	For extrapolation from rabbit 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 non-rodent (Gestation period in rabbits).
F4: Severe Toxicity (1-10)	5	Teratogenic effect with maternal toxicity observed in rabbits.
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOEL (50 mg/kg/day) value for Embryo toxicity selected.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{50 (NOAEL) x 50}}{\text{2.5 x 10 x 10 x 5 x 5}}$ = 0.4 mg/day

5. REFERENCES:

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205358Orig1s000lbl.pdf.
- https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9 & type=display.
- https://www.drugbank.ca/drugs/DB00819.
- https://www.medicines.org.uk/emc/product/2785/smpc.
- https://en.wikipedia.org/wiki/Acetazolamide.
- https://www.rivm.nl/bibliotheek/rapporten/650210003.pdf.
- http://www.inchem.org/documents/pims/pharm/acetazol.htm.
- https://pubchem.ncbi.nlm.nih.gov/compound/Acetazolamide#section=Acute-Effects.
- https://pfe-pfizercom-d8-prod.s3.amazonaws.com/products/material_safety_data/WP00031.pdf