PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR DIAZEPAM INJECTION BP 10 mg / 2 ml

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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 **Diazepam Injection BP 10 mg** 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:

Diazepam, first marketed as Valium, is a medicine of the benzodiazepine family that acts as an anxiolytic. It is commonly used to treat a range of conditions, including anxiety, seizures, alcohol withdrawal syndrome, muscle spasms, insomnia, and restless legs syndrome. It may also be used to cause memory loss during certain medical procedures. It can be taken orally (by mouth), as a suppository inserted into the rectum, intramuscularly (injected into muscle), intravenously (injection into a vein) or used as a nasal spray. When injected intravenously, effects begin in one to five minutes and last up to an hour.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

It is a colorless to light yellow crystalline compound, insoluble in water.

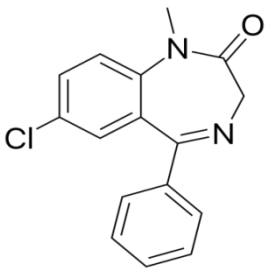
IUPAC Name: 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one

Chemical Abstract Services (CAS) Registry Number: 439-14-5

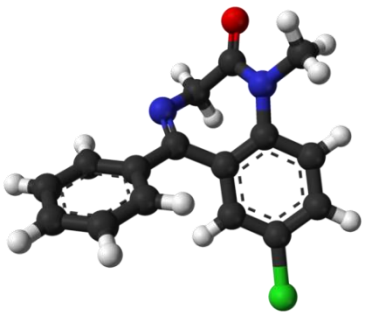
Molecular Weight: 284.74 g·mol−1

Chemical Formula: $C_{16}H_{13}ClN_2O$

Molecular Structure:



2D



3D

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4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
Toxicity	**Yes**	**No**	**Unknown**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmentaltoxicity	-	√	-
Highly sensitizingpotential	-	√	-

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5. SUMMARY OF ASSESSMENT PROCESS:

HAZARD IDENTIFICATION	
Pharmacodynamics data	Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle- relaxant, anticonvulsant and amnestic effects. Most of these effects are thought to result from facilitation of the action of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.
Pharmacokinetic data	Mechanism: Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. Benzodiazepines, such as diazepam, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABAs functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability. Absorption: After oral administration, it is considered that diazepam is rapidly and completely absorbed from the gastrointestinal tract as >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 – 1.5 hours with a range of 0.25 to 2.5 hours 15,16,6. Absorption is delayed and decreased when administered with a moderate fat meal 15. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting 15. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting 15. This results in an average decrease in Cmax of 20% in addition to a 27% decrease in AUC (range 15% to 50%) when administered with food. Volume of Distribution: In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. Protein Binding: Despite high binding to plasma proteins (98-99%) - mainly albumin and to a lesser extent α1-acid glycoprotein - diazepam is widely distributed into tissues and crosses the blood-brain barrier and is highly lipid soluble, which causes the initial effects to decrease rapidly as it is redistributed into fat deposits and tissues. Metabolism: Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam 15,16. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam 15,16. Temazepam and oxazepam are further largely eliminated by way of conjugation to glucuronic acid via glucuronidation 15,16. Furthermore, oxidation of diazepam is mediated by cytochrome P450 isozymes; formation of desmethyl-diazepam mainly by CYP2C19 and CYP3A and 3-hydroxy-diazepam (temazepam) and oxazepam by CYP3A. Because CYP2C19 is polymorphic, extensive metabolizers (EMs), and poor metabolizers (PMs) of diazepam can be distinguished 15,16. PMs of diazepam showed significantly lower clearance (12 vs 26 mL/min) and longer elimination half-life (88 vs 41 h) of diazepam than EMs after a single oral dose 15,16. Also, PMs had lower clearance, higher AUC and longer elimination half-life of desmethyl-diazepam.

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HAZARD IDENTIFICATION	
	Route of Elimination: Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates.
Acute toxicity	Oral LD_{50} of diazepam is 720 mg/kg in mice and 1,240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.
Repeated dose toxicity	In a forty-two week chronic toxicity study in rats diazepam was administered in doses up to and including 240 mg/kg/day; no abnormalities were observed on normal growth, food consumption, blood counts, gross and microscopic findings. **Duration, Species, Route, Dose, End Point, Target Organ** 6 Week(s) Mouse Oral 0.5 mg/kg LOAEL Male reproductive system 3 Month(s) Rat Oral 100 mg/kg/day NOAEL None identified 3 Month(s) Non-human Primate Oral 5 mg/kg/day LOAEL None identified 6 Month(s) Dog Oral 20 mg/kg/day LOAEL Liver 6 Month(s) Rat Oral 162 mg/kg/day LOAEL Kidney
Carcinogenicity	The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of hepatocellular tumours occurred in male mice. No significant increase in the incidence of tumours was observed in female mice, rats, hamsters or gerbils.
Genotoxicity studies	A number of studies have provided weak evidence of a mutagenic potential at high concentrations which are, however, far above therapeutic doses in humans.
Reproductive/Developmentaltoxicity	Reproduction studies in rats have been performed with diazepam in oral doses of 1, 10, 80, and 100 mg/kg/day. At the lower dose levels the survival of offspring was within normal limits. Further studies in rats at oral doses up to and including 80 mg/kg/day did not confirm a teratological effect on the offspring. At the 100 mg/kg dose level there was a decrease in the number of pregnancies and surviving offspring and several neonates showed skeletal or other defects.
Highly Sensitizing Potential	
Hazard Identification	

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IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and adverse effects	**Therapeutic Effects:** **Adverse Effects:** The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

NOAEL/NOEL/LOEL/ LOAEL	**Duration:** 6 Week(s) **Species:** Mouse **Route:** Oral **LOAEL:** 0.5 mg/kg

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	12	Based on the selection of toxicity study of Mouse.
F2: Inter-individual variability	10	Conventionally used to allow for differences between individuals in the human population
F3: Duration of toxicity	10	Short Term Study (6 Week) toxicity study in Mouse
F4: Severe toxicity (1-10)	1	No any toxicity
F5: NOAEL/NOEL/LOAEL/LOEL	10	Selection of LOAEL dose.
PK correction		For PDE calculation, no factor is applied.

PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{NOAEL (mg/day) x Body weight (kg)}}{\text{F1x F2 x F3 x F4 x F5}}$$

$$= \frac{0.5 \times 50}{12 \times 10 \times 10 \times 1 \times 10}$$

= **0.002 mg/day**

6. REFERENCES:

- https://go.drugbank.com/drugs/DB00829
- https://labeling.pfizer.com/ShowLabeling.aspx?id=4460
- https://pdf.hres.ca/dpd_pm/00025411.PDFs
- https://cdn.pfizer.com/pfizercom/products/material_safety_data/PZ00145.pdf

7. GLOSSARY:

PDE: Permitted daily exposure
AUC: Area under the curve **GRAS:**
Generally regarded as safe**GLP:** Good
laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
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 partof 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 concentrationthat 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 partthereof, 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 theliver 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 OECDguidelines 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.

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.