PERMITTED DAILY EXPOSURE FOR AMLODIPINE BESILATE

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 Amlodipine 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:

Amlodipine is a calcium channel blocker that dilates (widens) blood vessels and improves blood flow. It is used to treat chest pain (angina) and other conditions caused by coronary artery disease. Amlodipine is also used to treat high blood pressure (hypertension). Lowering blood pressure may lower your risk of a stroke or heart attack.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Amlodipine is a calcium channel blocker that dilates (widens) blood vessels and improves blood flow.

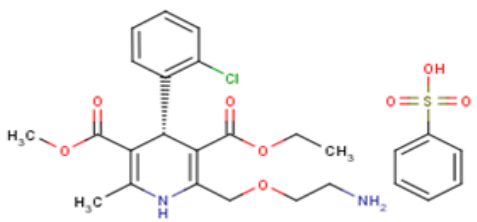
IUPAC NAME: 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

Chemical Abstract Services (CAS) Registry Number: 88150-42-9

Molecular Weight: 567.1 g/mol

Chemical Formula: $C_{20}H_{25}C_lN_2O_5.C_6H_6O_3S$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:

Pharmacodynamics data

Amlodipine works by blocking the voltage-dependent L-type calcium channels, thereby inhibiting the initial influx of calcium. Reduced intracellular calcium leads to decreased vascular smooth muscle contractility, increased smooth muscle relaxation, and resultant vasodilation. Ultimately, this causes a decrease in blood pressure.

Amlodipine is a dilator of peripheral arteries and arterioles which reduces the total peripheral resistance and, therefore, reduces the workload of the heart (afterload). The unloading of the heart is thought to decrease ischemia and relieve effort angina by reducing myocardial energy oxygen consumption and oxygen requirements.

Acute Toxicity

Species	Route	Dose (mg/ kg/day)	Animal per dose level	Duration	Findings
Dog	Oral (gavage)	4 8 16	2M	Single Dose	**At all dose levels:** Vasodilation and increases in plasma aldosterone levels. **At 4 mg/kg:** Compensatory tachycardia. **At 8 mg/kg:** In 1 of 2 dogs vomiting, sedation, respiratory distress and diarrhea 48 hr post-dose; normal at day 5. Compensatory tachycardia. **At 16 mg/kg:** Moribund with hyperthermia within 24 hours; low blood pressure returned to normal over 2-6 days; transient raise in heart rate. **Histological examination** showed congestion, edema and hemorrhage of the right atrial wall in the 2 dogs at 16 mg/kg. The hemorrhage in the right atrial wall corresponds to the right atrial lesions seen in long-term studies with amlodipine and other vasodilators (see long-term toxicity). One of 2 dogs at each dose showed fibrosis of the left ventricle in the subendocardial region and the posterior papillary muscle. The maximum tolerated dose was not determined.

PURE & CURE HEALTHCARE PVT. LTD., HARIDWAR	DETERMINATION OF PERMISSIBLE DAILY EXPOSURE (PDE) FOR AMLODIPINE BESILATE (ORAL DOSAGE)

SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Species	Route	Dose (mg/kg/day)	Animal per dose level	Duration	Findings
Mouse	Oral	2.5 5 10	10 M 10 F	2 Months	**At 10 mg/kg/day:** Mice died during week 2 of the study. **At 5 mg/kg/day (males and females) and 2.5 mg/kg/day (males):** Increase in water consumption. **At 5 mg/kg/day-Pathology:** Drug-related increases in heart and liver weights.
Rat	Oral	1.4 7 18	30 M 30 F	12 Months	Mortality: 3 rats (2 males and 1 female) at 18 mg/kg/day. At 18 mg/kg/day: Salivation, growth inhibition; Renal effects: increase in urinary volume with increased electrolytes excretion and decreased serum electrolytes; increase in BUN. At 7 mg/kg/day: Growth inhibition (males); Renal effects: increases of urinary volume and electrolyte excretion. Post-mortem: Increases of adrenal weights (at 18 mg/kg), increases of relative heart weight (18 and 7 mg/kg), dilated small intestines without morphological change (18 mg/kg). Histopathology - Main Finding: Enlargement of the zona glomerulosa of the adrenals (18 and 7 mg/kg).
Dog	Oral	0.125 0.25 0.5	4 M 4 F	12 Months	At 0.5 mg/kg/day: Reduction in blood pressure and increases in heart rate; increase in urinary volume and urinary excretion of electrolytes (females). At 0.5 mg/kg/day - Pathology: Showed inflammatory lesions of the right atrial wall in 1/8 dogs, similar to that of the 6 month study above, and diffuse gingival hyperplasia.

Carcinogenicity

There was no evidence of a carcinogenic effect when amlodipine was administered in the diet for up to 24 months to rats up to 2.5 mg/kg/day. Amlodipine was also administered for up to 24 months of dietary administration to mice at doses up to 2.5 mg/kg/day and no evidence of carcinogenicity was observed.

In vivo/In vitro Genotoxicity Studies

Study	Test Organism	Dose	Route	Major Findings
Ames Test (modified) Quantitative Plate Assay (QAP) and Metabolic Activation (MA) with Hepatic Microsomes	*Salmonella typhimurium*: Strains TA 1535, TA 1537, TA 98 and TA 100	10-0.02 mg/plate (QAP) 0.2-0.0005 mg/plate (MA)	*In vitro*	No evidence of mutation frequency.
In vivo Cytogenetic Tests	mouse bone marrow	20 mg/kg single dose 10 mg/kg/day for 5 days	*In vivo* PO SC	No indication of chromosome breakage or mutagenicity observed.
In vitro Cytogenetic Tests with or without metabolic activation [rat liver microsomal enzymes (S-9)]	human lymphocytes	Without metabolic activation: 0.01 to 1000 mcg/mL of culture medium With metabolic activation:	*In vitro*	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0 mcg/ml and below. At levels higher that 1.0 mcg/mL, compound produced mitotic inhibition. Activation: No drug induced clastogenic activity

SUMMARY OF HAZARD IDENTIFICATION:

			1.0 to 25 mcg/mL of culture medium.		observed at levels up to 10 mcg/ml. Higher levels produced mitotic inhibition.
	Quantitative Plate Assay (QAP) of Mouse Urine	*Salmonella typhimurium* Strains: TA 1535, TA 1537, TA 98 and TA 100.	0, 1, 10 and 20 mg/kg	*In vivo* PO	No incidence of an excreted mutagen.
	L 5178Y/TK +/- Gene Mutation Assay with and without liver S-9 fraction	Mouse lymphoma cells	1.2 - 38 mcg/mL	*In vitro*	No evidence of gene mutational activity.

Reproductive/Developmental Toxicity

Species	Route	Dose (mg/kg/day)	Animal per dose level	Duration	Findings
Fertility					
Rat (SD) (Japanese Study)	Oral (gavage)	1.4 7 18	24 M + 24 F	Males 71 days prior to and during mating. Females 14 days prior to and during mating and up to 7 days of gestation.	At 18 mg/kg: Impairment of body weight gain (females). There were no effects of the drug on copulation or pregnancy rates, nor any evidence of embryotoxicity or teratogenicity.
Teratology					
Rat (Charles River CD/SD)	Oral (gavage)	2 5 10	20 F	Days 6-15 post insemination. Hysterectomies on day 20 of gestation.	No effects were observed.
Rat (SD) Japanese Study	Oral (gavage)	3 7 18	34 F	Days 7-17 post-insemination. 2/3 of dams sacrificed on day 21 of gestation. F1 generation followed.	No effects were observed except in the dams. At 18 mg/kg: Reduction in food intake and body weight gain.
Rabbit (Japanese White) Japanese Study	Oral	3 7 18	18 or 19 F	Day 6 to day 18 of gestation.	At 18 and 7 mg/kg: Decrease in maternal body weight (18 mg/kg) decrease in food consumption (18 and 7 mg/kg). No evidence of drug induced fetotoxicity or teratogenicity.
Pre and Post Natal					
Rat (SD) Japanese Study	Oral (gavage)	1.4 2.8 7.0	25 F	Day 17 of gestation to day 21 post-partum.	As in the combined Fertility/Perinatal Study above; at the high dose level (7.0 mg/kg/day) adverse effects were observed on parturition and number of viable pups at birth and day 4 post-partum.

Highly Sensitizing Potential	Amlodipine does not comes under the category of Highly Sensitizing Potential chemicals.

PURE & CURE HEALTHCARE PVT. LTD., HARIDWAR	DETERMINATION OF PERMISSIBLE DAILY EXPOSURE (PDE) FOR AMLODIPINE BESILATE (ORAL DOSAGE)

SUMMARY OF HAZARD IDENTIFICATION:	
IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any adverse effect observed due to sensitivity.
Clinical therapeutic and adverse effects	For both hypertension and angina, the recommended initial dose of Sandoz Amlodipine (Amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily. **Therapeutic Dose Adults:** 5 mg/day (0.1 mg/kg/day) The significant adverse effects of amlodipine include peripheral edema, heart failure, pulmonary edema, flushing, dizziness, headache, drowsiness, skin rash, nausea, and abdominal pain.

NOAEL/LOAEL

Repeated Dose Toxicity					
Duration	**Species**	**Route**	**Dose (mg/kg/day)**	**End point**	**Target Organ**
3 M	Rat	Oral	3	NOAEL	Adrenal gland & Heart
1 Year			2		
Reproduction & Development Toxicity					
Fertility & Embryonic Development	Rat	Oral	25	NOAEL	Not Teratogenic, Maternal Toxicity
Peri/Postnatal Development	Rat	Oral	4	NOAEL	Fetotoxicity & Fetal Mortality
Prenatal & Postnatal Development	Rat	Oral	25	NOAEL	Not Teratogenic
Prenatal & Postnatal Development	Rabbit	Oral	25	NOAEL	Not Teratogenic
Genotoxicity					
Study type		**Cell Type/Organism**			**Result**
In Vitro [Bacterial Mutagenicity (Ames)]		Salmonella, *E.coli*			Negative
In Vivo (Cytogenetics)		Mouse Bone Marrow			Negative
In Vitro (Chromosome Aberration)		Human Lymphocytes			Negative
Carcinogenicity					
Duration	**Species**	**Route**	**Dose (mg/kg/day)**	**End Point**	**Effects**
24 M	Rat	Oral (in feed)	2.5	NOAEL	Not Carcinogenic, No effects at maximum dose
24 M	Mouse	Oral (in feed)	0.5	NOAEL	Not Carcinogenic

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	**1**	For 24-month study in rodents in repeat dose toxicity
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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{0.5\ (\text{NOAEL}) \times 50}{5 \times 10 \times 1 \times 1 \times 5}$ = 0.1 mg/day

5. REFERENCES:

- https://www.drugbank.ca/drugs/DB00381.
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Amlodipine%20Product%20Monograph.pdf.
- https://pfe-pfizercom-prod.s3.amazonaws.com/products/material_safety_data/amlodipine_besylate_tabs_8-Aug-2018.pdf.
- https://www.healthline.com/health/amlodipine/oral-tablet#other-warnings.