PERMITTED DAILY EXPOSURE FOR RAMIPRIL

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 Ramipril 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:

Ramipril is a medication used to treat high blood pressure, heart failure, and diabetic kidney disease. Also used to prevent cardiovascular disease in those at high risk. It is a reasonable initial treatment for high blood pressure. It is taken by mouth.

Common side effects include headaches, dizziness, feeling tired, and cough. Serious side effects may include liver problems, angioedema, kidney problems, and high blood potassium. Use in pregnancy and breastfeeding is not recommended. It is an ACE inhibitor and works by decreasing renin-angiotensin-aldosterone system activity.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

A white to off-white crystalline powder with a melting point of 105°C to 112°C. Slightly soluble in water, and freely soluble in ethanol and methanol.

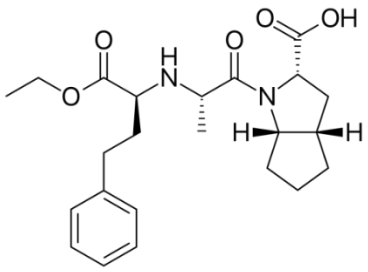
IUPAC name: (2S,3aS,6aS)-1-[(2S)-2-[[(2S)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3a,4,5,6,6a-hexahydro-2H-cyclopenta[b]pyrrole-2-carboxylic acid

Chemical Abstract Services (CAS) Registry Number: 87333-19-5

Molecular Weight: 416.518 g·mol−1

Chemical Formula: $C_{23}H_{32}N_2O_5$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Administration of Ramipril to patients with mild to moderate essential hypertension results in a reduction of both supine and standing BP usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt-and/or volume-depleted. In single dose studies, doses of 5-20 mg of Ramipril lowered BP within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. At recommended doses given once daily, antihypertensive effects have persisted over 24 hours. The effectiveness of Ramipril appears to be similar in the elderly (> 65 years of age) and younger adult patients given the same daily doses. In studies comparing the same daily dose of Ramipril given as a single morning dose or as a twice daily dose, BP reductions at the time of morning trough blood levels were greater with the divided regimen. While the mechanism through which Ramipril lowers BP appears to result primarily from suppression of the renin- angiotensin- aldosterone system (RAAS), Ramipril has an antihypertensive effect even in patients with low-renin hypertension. The antihypertensive effect of ramipril and thiazide diuretics used concurrently is greater than that seen with either agent used alone. Abrupt withdrawal of ramipril has not resulted in rapid increase in BP.
Pharmacokinetics data	**Absorption:** Following oral administration, Ramipril is rapidly absorbed with peak plasma concentrations occurring within 1 hour. The extent of absorption of Ramipril is 50-60% and is not significantly altered by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced. Following a single administration of up to 5 mg of Ramipril, plasma concentrations of Ramipril and Ramipril at increase in a manner that is greater than proportional to dose; after a single administration of 5 mg to 20 mg of Ramipril the plasma concentrations for both are dose proportional. The non-linear pharmacokinetics observed at the lower doses of Ramipril can be explained by the saturable binding of Ramipril at to ACE. At steady-state, the 24-hour AUC for Ramipril at is dose-proportional over the recommended dose range. The absolute bioavailabilities of Ramipril and Ramipril at were 28% and 44% respectively when 5 mg of oral Ramipril was compared to 5 mg given intravenously. Plasma concentrations of Ramipril at decline in a triphasic manner. The initial rapid decline, which represents distribution of the drug, has a half life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, Ramipril at shows 2 elimination phases. The apparent elimination phase has a half-life of 9-18 hours, and the terminal elimination phase has a prolonged half-life of >50 hours. After multiple daily doses of Ramipril 5-10 mg, the half-life of Ramipril at concentrations was 13-17 hours, but was considerably prolonged at 2.5 mg (27-36 hours). After once daily dosing, steady-state plasma concentrations of Ramipril at are reached by the 4th dose. Steady-state concentrations of Ramipril at are higher than those seen after the 1st dose of Ramipril especially at low doses (2.5 mg). **Distribution:** Following absorption, Ramipril is rapidly hydrolyzed in the liver to its active metabolite, ramipril at. Peak plasma concentrations of ramipril at are reached 2-4 hours after drug intake. The serum protein binding of ramipril is

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

SUMMARY OF HAZARD IDENTIFICATION:

about 73% and that of ramipril at is 56%. Metabolism: Ramipril is almost completely metabolized to the active metabolite ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramipril at, all of which are inactive.

Excretion: After oral administration of ramipril, about 60% of the parent drug and its metabolites is excreted in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Acute Toxicity

Below are summarized species-specific LD50 values for both oral and intravenous (IV) administrations of ramipril.

Route	Species	Sex	LD_{50} (mg/kg)
Oral	Mouse	M	10933
		F	10048
	Rat	M	>10000
		F	>10000
	Dog	M	>1000
Intravenous	Mouse	M	1194
		F	1158
	Rat	M	688
		F	609

The symptoms observed in mice were decreased spontaneous activity, crouching, hypothermia, dyspnea, and clonic convulsions; deaths occurred within 30 minutes after IV and 24 hours after oral administration. In survivors, the symptoms disappeared by 1 - 5 days after administration; necropsies revealed no abnormality in any of the surviving animals. In rats, reduced spontaneous activity was noted (oral administration), while after IV administration similar signs occurred as in mice; the sign of lethal toxicity was clonic convulsions (IV administration).

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Mouse	28 days 90 days	2M, 2F 3M, 3F	Oral	1000	Reduced erythrocytes, hemoglobin, hematocrit, increased reticulocytes. Hyperplasia of juxtaglomerular apparatus.
Rat	30 days	10-15M 10-15F	Oral	2.5, 80, 2500	At all doses: decrease in body weight, reduced liver weight, increased kidney weight. At ≥80 mg/kg/d: Reduced heart weight. At 2500 mg/kg/d: Reduced erythrocytes, hematocrit and bilirubin, increased BUN.
Rat	3 months	10-15M 10-15F	Oral	2.5, 80, 500	At all doses: Reduced chloride and glutaminic-oxalacetic transaminase (GOT), increased phosphorus and blood urea nitrogen (BUN). At 80 mg/kg/d: Reduced heart, liver, prostate weights, increased kidney weight. Atrophic segments of renal tubules. Increased serum creatinine. At 500 mg/kg/d: Reduced body and heart weights, increased kidney and adrenal weights. Reduced erythrocytes, hemoglobin, hematocrit, increased bilirubin. Increased number of atrophic renal tubular segments. Moderate gastric mucosa necroses
Rat	3 months	10M, 10F	Oral	500, 1/3 Ringer solution for drinking	Increased number of tubular atrophies.
Rat	6 months	10-20M 10-20F	Oral	0.1, 0.25, 3.2, 40, 500	At all doses: Serum bilirubin increased, reduced heart weight. At ≥ 40 mg/kg/d: Increased kidney weight. Reduced erythrocytes, hemoglobin, hematocrit, increased BUN. Distal tubular atrophies, fibromuscular pad formations in gastric mucosa/muscularis not proliferative in nature.
Rat	6 months	20M, 20F	Oral	3.2, 40, 500, 1/3 Ringer solution for drinking	All doses: Fibromuscular or solitary pad formation in gastric fundus mucosa/muscularis

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

SUMMARY OF HAZARD IDENTIFICATION:

	Rat	18 months	20-25M 20-25F	Oral	0.25, 3.2, 40, 500	At ≥3.2 mg/kg/d: Fibromuscular pads in gastric fundus mucosa, focal atrophies in renal cortex, partly with cysts. At ≥40 mg/kg/d: Anemia, increased BUN and serum creatinine, urinary epithelial cells. Reduced heart weight and increased kidney and adrenal weight.
	Dog	30 days	2M, 2F	Oral	3.2, 32	No pathological findings
	Dog	3 months	3-4M 3-4F	Oral	3.2, 32, 320	At 320 mg/kg/d: Anemia, increased BUN and serum creatinine, impaired erythropoiesis. Juxtaglomerular hyperplasia.
	Dog	6 months	6M, 6F	Oral	3.2, 32, 320	At 32 mg/kg/d: Anemia, juxtaglomerular hyperplasia. At 320 mg/kg/d: Reduced body weight. Increased BUN and serum creatinine. Distal tubular atrophies with round cell infiltrations. Anemia, juxtaglomerular hyperplasia.
	Dog	12 months	6M, 6F	Oral	2.5, 25, 250	At all doses: Reduced body weight. At ≥25 mg/kg/d: Anemia and leukopenia, impaired erythropoiesis, increased hemosiderin deposition in liver and spleen, juxtaglomerular hyperplasia. At 250 mg/kg/d: Increased BUN and serum creatinine.
	Monkey	6 months	4-5M 4-5F	Oral	0.5, 16, 500	At ≥16 mg/kg/d: Increased BUN, juxtaglomerular hyperplasia. Reduced body weight. At 500 mg/kg/d: Diarrhea, anemia, increased serum creatinine, some urinary casts, leukocytes and epithelial cells.
	Monkey	6 months	5M 5F	Oral	2, 8	No pathological findings.

Carcinogenicity

Species	No. of animals per group	Dose (mg/kg/day)	Duration of dosing	Results

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

SUMMARY OF HAZARD IDENTIFICATION:

	Rat (Wistar)	32M, 32F	5, 50, 500	M 60 days before mating F 14 days before mating to end of lactation	At ≥50 mg/kg/d: Parents renal pelvis enlargement, offspring light brown discolouration of kidney tissue and dilatation of renal pelvis. At 500 mg/kg/d: Parents yellow white colouring and induration of renal marrow. Fertility normal.
	Rat (Wistar)	20F	10, 100, 1000	Days 7-17 of gestation	At 1000 mg/kg/d: Reduced food consumption of mothers, reduced body weight gains of young. One young circular non-ossified area in supraoccipital bone, 1 young distortion of right scapula. No teratogenic effects.
	Rat (Wistar)	20-30F	0.32, 1.25, 5, 10, 100, 1000	Day 17 of gestation to day 21 of lactation	At ≥100 mg/kg/d: Decreased gestation body weight of young, enlarged to day 21 renal pelvis up to hydronephrosis with light brown coloring of renal cortex and marrow.
	Rat (Sprague Dawley)	20F	100	Day 17 of gestation to day 21 of lactation	Young: Enlarged renal pelvis and light brown coloration of kidney tissue.
	Rabbit (Himalayan)	15F	0.4, 1, 2.5	Day 6 to day 18 of gestation	At 0.4 mg/kg/d: 1 abortion, 1 foetus with diaphragm hernia. At 1 mg/kg/d: 1 abortion, 1 premature delivery, 2 animals died, no animals gained weight. One dead foetus with possible hydrocephalus. At 2.5 mg/kg/d: 2 animals died, no animals gained weight, 1 foetus with diaphragm hernia, 1 with first cervical aplasia and aplasia of 1 thorax vertebra and 1 rib pair
	Monkey (Cynomolgus)	4-13F	5, 50, 500	Days 20- 25 of gestation	At all doses: No sign of teratogenesis. At 5 mg/kg/d: 2 abortions, 7 diarrhea, 2 vomiting, 10 weight loss. At 50 mg/kg/d: 1 animal died, 3 abortions, 7 diarrhea, 2 vomiting, 10 weight loss. At 500 mg/kg/d: 3 animals died, 1 abortion, 4 weight loss, 4 vomiting, 4 diarrhea.

In vivo/In vitro Genotoxicity Studies	Ramipril was not mutagenic in the Ames microbial mutagen test, the HGPRT test in V79 cells, the micronucleus test in mice and the UDS test in human A549 cells.
Reproductive/Developmental Toxicity	There was no evidence of a carcinogenic effect when ramipril was administered for 104 weeks to NMRI mice at doses ≤1000 mg/kg/day and to Wistar rats at doses ≤500 mg/kg/day
Highly Sensitizing Potential	Ramipril has been linked to increased sun **sensitivity** and rash.

PERMITTED DAILY EXPOSURE FOR RAMIPRIL

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	**Clinical Therapeutic dosage:** Hypertension: Initial 2.5 mg once daily in patients not receiving diuretic therapy. In patients receiving a diuretic, initiate ramipril at 1.25 mg once daily. Usual maintenance dosage: 2.5–20 mg daily. Heart Failure: Initially 2.5 mg twice daily. If hypotension occurs, reduce dosage to 1.25 mg twice daily. After 1 week at initial dosage, adjust dosage as tolerated at 3-week intervals to target dosage of 5 mg twice daily. **Adverse Effect:** Headache, Cough, Tired feeling, Dizziness, Spinning sensation, Malaise Nausea, Vomiting & Stomach discomfort.

NOAEL/LOAEL	0.025 mg/kg/day considered as NOAEL.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	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	18 month 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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{0.025\ (\text{NOAEL}) \times 50}{1 \times 10 \times 1 \times 1 \times 5}$ = 0.025 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Ramipril
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Ramipril_Tab_PM_English_20151214.pdf