# PERMITTED DAILY EXPOSURE FOR LOSARTAN POTASSIUM

## 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 Losartan Potassium 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:

Losartan is a medication mainly used to treat high blood pressure. It is also used for diabetic kidney disease, heart failure, and left ventricular enlargement. It is taken by mouth. It may be used alone or in addition to other blood pressure medication. Up to six weeks may be required for the full effects to occur.

Common adverse effects include muscle cramps, stuffy nose, cough, high blood potassium and anemia. Severe adverse effects may include angioedema, low blood pressure, and kidney problems. Use during pregnancy may result in harm to the baby. Use is not recommended during breastfeeding. It is in the angiotensin receptor blocker family of medication. It works by blocking angiotensin II.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

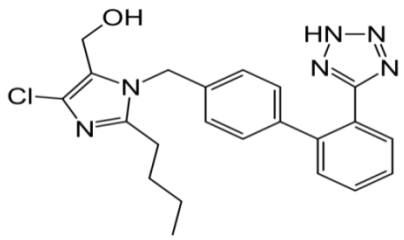
**IUPAC name:** (2-butyl-4-chloro-1-{[2'-(2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazol-5-yl)methanol

**Chemical Abstract Services (CAS) Registry Number:** 114798-26-4

**Molecular Weight:** 422.91 g/mol g·mol−1

**Chemical Formula:** $C_{22}H_{23}ClN_6O$

**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: | |
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| **Pharmacodynamics data** | Losartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity, and a consequent rise in angiotensin II plasma concentration, in hypertensive patients. Maximum blood pressure lowering, following oral administration of a single dose of losartan, as seen in hypertensive patients, occurs at about 6 hours. In losartan-treated patients during controlled trials, there was no meaningful change in heart rate. There is no apparent rebound effect after abrupt withdrawal of losartan therapy. Black hypertensive patients show a smaller average blood pressure response to losartan mono therapy than other hypertensive patients. |
| **Pharmacokinetics data** | **Absorption:** Following oral administration, losartan is well absorbed, with systemic bioavailability of losartan approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite, although about 1% of subjects did not convert losartan efficiently to the active metabolite. Mean peak concentrations of losartan occur at about one hour, and that of its active metabolite at about 3-4 hours. Although maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than that of losartan.<br><br>**Distribution:** Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all. The volume of distribution of losartan is about 34 liters, and that of the active metabolite is about 12 liters.<br><br>**Metabolism**: Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite, E-3174, COZAAR® (losartan potassium) Page 15 of 38 that is responsible for most of the angiotensin II receptor antagonism that follows oral losartan administration. Various losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, E-3174, several inactive metabolites are formed. In vitro studies indicate that the cytochrome P450 isoenzymes 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.<br><br>**Excretion:** The terminal half-life of losartan itself is about 2 hours, and that of the active metabolite, about 6-9 hours. The pharmacokinetics of losartan and this metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily administration. Total plasma clearance of losartan is about 600 mL/min, with about 75 mL/min accounted for by renal clearance. Total plasma clearance of the active metabolite is about 50 mL/min, with about 25 mL/min accounted for by renal clearance. Both biliary and urinary excretion contribute |

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substantially to the elimination of losartan and its metabolites.

**Acute Toxicity**

| Organism | Test type | Route | Dose mg/kg | Effect | Reference |
|---|---|---|---|---|---|
| Man | TDLo | Oral | 21.428 | Liver: liver function tests impaired; liver: other changes | JAMA, Journal of the American Medical Association ., 278(1572), 1997 [PMID:9370501] |
| Man | TDLo | Oral | 18 | Sense organs and special senses: change in function: taste | Annals of Internal Medicine., 129(72),1998 |
| Man | TDLo | Oral | 7 | Sense organs and special senses: change in function: taste; lungs, thorax, or respiration: cough; gastrointestinal: other changes | Annals of Internal Medicine., 129(72), 1998 |
| Women | TDLo | Oral | 42 | Gastrointestinal: hypermotility, diarrhea; kidney, ureter, and bladder: changes in tubules (including acute renal failure, acute tubular necrosis); kidney, ureter, and bladder: urine volume decreased | Annals of Internal Medicine., 124(775), 1996 |
| Man | TDLo | Oral | 17.5 | Sense organs and special senses: change in function: taste | Lancet., 347(471), 1996 [PMID: 8618505] |

The oral TDLO in mice is 1000mg/kg and in rats is 2000mg/kg. [L7423,L7426] In humans the TDLO for men is 10mg/kg/2W and for women is 1mg/kg/1D.[L7441] Symptoms of overdose are likely to include hypotension, tachycardia, or bradycardia due to vagal stimulation. [L7423,L7426] Supportive treatment should be instituted for symptomatic hypotension.[L7423,L7426] Hemodialysis will not remove losartan or its active metabolite due to their high rates of protein binding.[L7423,L7426]

**Human Exposure Studies:** In this preliminary, single-dose, open-label, cross-over study conducted in 12 healthy volunteers, psychomotor assessment was carried out by four tests: Simple reaction time (SRT), multiple choice reaction time test (MCRT), critical flicker fusion frequency threshold test (CFFT), and tracking performance test (TPT). Each volunteer received a single dose of each of the three test drugs with a washout period of 10 days between different test sessions and then evaluated for post-drug scores at 2-hr intervals up to 12 hr and then at 24 hr. The changes from the baseline scores by the test drug were statistically analyzed. All the three antihypertensive drugs caused significant improvement in a similar fashion on SRT, MCRT calculated as error index, CFFT, and TPT. Aliskiren caused numerically more improvement than the other two test drugs, suggesting better cognitive profile. However, inter-drug

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| | comparisons were non significant. The results of the study highlight improvement of the cognitive functions equally by ramipril, losartan, and aliskiren. The results of the study could be of immense clinical utility in ambulatory hypertensive patients especially engaged in sensory-motor coordination tasks like driving and operating on mechanical tools. |

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## SUMMARY OF HAZARD IDENTIFICATION:

**Repeated Dose Toxicity (Chronic Toxicity)**

The toxic potential of Losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

### Oral Administration:

| Species | Duration | No. of animals/Group | Dose (mg/kg/day) | Effects |
|---|---|---|---|---|
| Rat (Sprague-Dawley Crl:CD (SD) BR) | 5 weeks | 12 M + 12 F | 0, 15, 45, 135 | Mid- and high-dose males: slight decrease in body weight gain. High-dose males: slight decrease in red blood cell count. Males all dosage levels: decrease in heart weight. High-dose groups: slight increases in BUN; focal gastric lesions. Mid- and high-dose groups: slight increase in serum chloride. All dosage levels: slight increases in serum glucose |
| Rat (Sprague-Dawley Crl:CD (SD) BR) | 14 weeks | 17 M + 17 F | 0, 15, 45, 135 | Mid- and high-dose males: slight decreases in the rate of body weight gain; increase in BUN; grossly evident focal lesions in the gastric mucosa. High-dose males: slight decreases in RBC parameters; increase in cholesterol; alkalinization of the urine. Males all dosage levels: decrease in heart weight. High-dose females: increase in BUN. High-dose groups: increase in sodium, chloride, and/or potassium |
| Rat (Sprague-Dawley Crl:CD (SD) BR) | 53 weeks | 30 M + 30 F | 0, 15, 45, 135 | High-dose males: slight decrease in erythrocyte parameters (week 25); slight increase in serum phosphorus (week 25); focal erosions of the glandular mucosa of the stomach (also noted in one low-dose male). Mid- and high-dose males: increases in BUN; decreased heart weight and heart weight relative to brain weight (at terminal necropsy); very slight hyperplasia of juxtaglomerular cells (at interim necropsy). High-dose females: increases in BUN; decreased absolute heart weight and heart weight relative to brain weight (at interim necropsy). Mid- and high-dose females: slight decreases in food consumption; slight decrease in erythrocyte parameters (high-dose week 39, mid-dose weeks 39 and 51). All females: decreases in serum triglycerides. All groups: decreases in urinary protein; very slight juxtaglomerular cell hyperplasia; lower incidence and severity of spontaneous chronic nephritis. Mid- and high-dose groups: postdose salivation (weeks 11 and 20). High-dose groups: decrease in body weight gain. |
| Dog (Beagle) | 14 weeks | 5 M + 5 F | 0, 5, 25, 125 H | High-dose males: slight decrease in erythroid parameters. High-dose groups: gastrointestinal toxicity (emesis, abnormal stool colour and consistency, fecal occult blood); slight decrease in heart weight. Mid-dose groups: excessive salivation and emesis. No treatment-related effects |

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## SUMMARY OF HAZARD IDENTIFICATION:

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| | | | | | on body weight, food consumption, clinical pathology, electrocardiography, physical exams, ophthalmoscopic exams, or gross and microscopic postmortem findings. |
| | Dog (Beagle) | 53 weeks | 8 M + 8 F | 0, 5, 25, 125 | High-dose groups: predose and/or postdose hypersalivation; occasional emesis and change in stool consistency and colour. Mid- and high-dose groups: sporadic, isolated increases in serum ALT. No treatment-related alteration in body weight or food consumption, ophthalmologic findings or changes in electrocardiographic, hematologic, or urinalysis parameters. No treatment-related mortality |
| | Monkey [Rhesu (Macaca mulatta)] | 14 weeks | 4 M + 4 F | 0, 20, 100, 300 | High-dose group: slight decrease in erythrocyte parameters (weeks 8 and 11); slight decrease in BUN (week 11); increase in angiotensin II levels (24 hours postdose); tarry intestinal contents and small depressed, reddened foci in the stomach and/or small intestine (at necropsy). No treatment-related physical signs, mortality, or changes in food consumption, body weight, ophthalmic exams, or urinalysis. No treatment-related changes in organ weights. |
| | **I.V. Administration** | | | | |
| | Rats (Sprague-Dawley Crl:CD (SD) BR) | 16 days | 15 M + 15 F | 0, 0.92, 4.59, 9.17 | High-dose males: slight decreases in erythrocyte count and hematocrit. No treatment-related deaths, clinical signs, or changes in body weight gain, food consumption, ophthalmology, serum biochemistry, or urinalysis |
| | Rats (Sprague-Dawley Crl:CD (SD) BR) | 15 days | 15 M + 15 F | 0, 1, 5, 10† | Mid- and high-dose males: slight decrements in body weight. All groups: slight decrease in heart weight; slight decrease in mean terminal body weight. No treatment-related effects on food consumption, ophthalmologic exams, hematology, serum biochemical determinations, or urinalysis. |
| | Dogs (Beagle) | 17 days | 4 M + 4 F | 0, 0.92, 4.59, 9.17 | No drug-related deaths, no drugrelated **clinical signs, and no drugrelated changes in body** weight gain, food consumption, ophthalmology, electrocardiography, hematology, serum biochemistry and urinalysis. No treatment-related changes in organ weight or gross microscopic changes. |
| | Dogs (Beagle) | 15 days | 4 M + 4 F | 0, 1, 5, 10 | No drug-related deaths, no drugrelated clinical signs, and no drugrelated changes in body weight gain, food consumption, ophthalmology, electrocardiography, hematology, serum biochemistry and urinalysis. No treatment-related changes in organ weight or gross microscopic changes |
| **Carcinogenicity** | **Laboratory Animals:** Chronic Exposure or Carcinogenicity/Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic | | | | |

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| | acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day. |
| **In vivo/In vitro Genotoxicity Studies** | Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the in vitro alkaline elution and in vitro chromosomal aberration assays. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m2 ). In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, in vitro alkaline elution, and in vitro chromosomal aberration assays. |
| **Reproductive/Developmental Toxicity** | **Laboratory Animals**: Developmental or Reproductive Toxicity/ Previous developmental and reproductive toxicity studies in rats with losartan, a potent AT1-selective angiotensin II (AII) receptor antagonist, correlated maternal treatment during gestation day (GD) 15-20 with irreversible renal abnormalities in the F1 generation. Continued treatment through lactation was also associated with increases in pup mortality and decreases in pup body weights that persisted through weaning. The studies presented here were undertaken to quantify fetal and neonatal exposure to losartan when administered to the dam by oral gavage during early gestation, late gestation, and lactation. Following daily oral dosing of 135 mg/kg/day on GD6-15, fetal drug levels were negligible. However, losartan and its active metabolite, EXP3174 (L-158,641) were readily detectable in fetal plasma on GD 20 (estimated AUC values, 50.70 and 167.70 ug/hr/mL, respectively) and maternal milk during lactation (1.61 and 1.67 ug/mL, respectively). These studies suggest that the relative increased sensitivity of the fetus as compared to the neonate for losartan-induced renal lesions is related to the degree of exposure which is dependent on the time of administration (early gestation vs. late gestation/lactation) and the route of exposure (transplacental or through the milk). Furthermore, the maximum exposure to losartan and EXP3174 correlates with the ontogeny of the renin angiotensin system on approximately GD 17 and the critical period for losartan-induced renal lesions (GD15-20). The data support the hypothesis that the observed adverse fetal and neonatal effects are pharmacologically mediated, presumably through the lack of AT1 receptor stimulation.<br><br>**Laboratory Animals:** Developmental or Reproductive Toxicity/ Fetal cardiac development includes rapid formation of a three-dimensional collagen network, composed mainly of type I and III fibrillar collagens. Collagen fibrils have been found in cardiac jelly at very early stages of cardiac development and are thought to have structural and functional properties. In adult rat cardiac tissue, angiotensin II (AngII) via AT1 receptor binding and AngII-regulated expression of transforming growth factor beta-1 (TGF-beta 1) each upregulate collagen transcription. AT1 and AT2 receptor subtypes are developmentally regulated; both have been localized in fetal tissue where the AT2 receptor is considered a determinant of morphogenesis. We sought to determine whether blockade of either |

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| **SUMMARY OF HAZARD IDENTIFICATION:** | |
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| | receptor would result in attenuation of collagen mRNA expression and fibrillar collagen accumulation and alter TGF-beta 1 mRNA expression in the developing fetal heart examined at birth. Pregnant rats were treated either with an AT1 receptor antagonist losartan or an AT2 receptor antagonist PD123319 and compared with untreated age-matched controls. Offspring were studied within 24 h of birth. Type I and type III collagen mRNA expression, as well as TGF-beta 1 mRNA expression, were examined by in situ hybridization. Collagen concentration was determined spectrophotometrically by picrosirius red staining and type I and III collagens were detected by immunoblotting. We found: (1) comparable birth weights in control and PD123319-treated animals, but reduced body weight in newborn losartan-treated animals; (2) compared to untreated animals, type I collagen and TGF-beta 1 mRNA expression in cardiac tissue were each equally reduced in both losartan and PD123319-treated animals; (3) increased type III collagen mRNA expression in both PD123319- and losartan-treated groups; and (4) a significant decrease in total soluble cardiac collagen concentration in both losartan and PD123319-treated groups, confirmed by attenuated immunoreactivity of type I and III collagens in whole heart extracts by Western blotting. The results of these pharmacologic interventions suggest AngII receptors are expressed in cardiac tissue during gestation, where both AT1 and AT2 receptors are involved in the regulation of type I and III collagen expression and structural protein accumulation. These effects appear to be mediated, in part, by attenuated cardiac TGF-beta 1 levels. The marked decrease in newborn cardiac collagen content has yet undefined functional consequences.<br><br>**Laboratory Animals:** Developmental or Reproductive Toxicity/ The angiotensin type 1 (AT1) receptor antagonist, losartan (10 mg/kg) was infused intravenously into nine chronically catheterized fetal sheep (125-132 days gestation). Losartan reduced the fetal systolic (P <0.01) and diastolic (P <0.01) pressor response to 5 microg angiotensin II (AngII) i.v. from 27.4 +/- 1.5 to 7.4+/-0.9 and from 17.5 +/- 1.3 to 5.4 +/- 0.6 mm Hg, respectively, after 1 hr and to 6.1 +/- 0.5 and 4.4 +/- 0.5 mm Hg, respectively, after 2 hr. Maternal pressor responses to 5 microg AngII i.v. were unchanged. Fetal mean arterial pressure decreased (P <0.05) after losartan administration, but fetal heart rate did not change. 2. Fetal haematocrit increased (P <0.05), fetal PO2 decreased (P <0.01), PCO2 did not change and pH decreased (P <0.01), as did plasma bicarbonate levels (P <0.01) following administration of losartan. Thus, losartan induced a fetal metabolic acidosis. 3. Fetal placental blood flow did not change following administration of losartan. In the fetal kidney, losartan caused a decrease in vascular resistance (P <0.01) and an increase in blood flow (P <0.05). Glomerular filtration rate decreased (P <0.05); thus, filtration fraction decreased (P <0.01). There was no change in the fractional reabsorption of sodium and glomerulotubular balance was maintained. Free water clearance decreased (P <0.01) and became negative. Urine flow decreased (P <0.01), the excretion rates of sodium, potassium and chloride did not change, but the urinary sodium: potassium ratio decreased (P <0.05). There was a decrease in lung liquid flow (P <0.05) following losartan. 4. It is concluded that the fetal renin-angiotensin |

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| | system (RAS) is important in the maintenance of fetal arterial pressure, the regulation of fetal renal blood flow and is essential in the maintenance of fetal glomerular function. Further, these actions of AngII are mediated via functional AT1 receptors. These effects of losartan on the fetal cardiovascular system, renal blood flow and function are similar to those observed following captopril administration. Thus, the effects of angiotensin converting enzyme (ACE) inhibition in the foetus are due to the blockade of the fetal RAS and are independent of any direct effects on bradykinin or prostaglandin levels.<br><br>**Case Reports:** The fetotoxic effects of angiotensin converting enzyme inhibitors when used during the second half of pregnancy are well known. The more recently developed angiotensin II receptor antagonists appear to yield similar fetal abnormalities. We report a premature infant born to a 41-year-old mother with a long history of infertility who had received losartan therapy for hypertension throughout an undetected pregnancy. Ultrasound examination 2 days prior to delivery identified a single fetus at 29 weeks gestation, anhydramnios, and an empty fetal bladder. The neonatal course was complicated by oliguria, hyperkalemia, marked renal dysfunction, respiratory failure, joint contractures, and a large anterior fontanelle with widely separated sutures. Hypotension (mean arterial pressure <25 torr) on day 1 responded to volume expansion, dopamine, and hydrocortisone. Serum creatinine reached a maximum of 2.7 mg/dL on day 6 and decreased to 0.4 by day 56. No formal urinalysis was performed, but the urine was reported to be visually clear throughout the course. Although a renal ultrasound on day 2 was normal, a follow-up study at 7 months revealed bilateral generalized parenchymal echogenicity, consistent with medical renal disease. Since then, weight and length have been at the 5th percentile or less, with apparent renal tubular acidosis necessitating the addition of sodium citrate supplements.<br><br>**Teratology:** Losartan potassium has been shown to produce adverse reactions in rat fetuses and neonates. The reactions include decreased body weight, mortality and/or renal toxicity. Pharmacokinetic evaluation of fetal plasma showed significant levels of losartan and its active metabolite, E-3174 (L-158,641), on Gestation Day 20 compared to negligible value on Gestation Day 15. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on these findings, the fetal and neonatal effects of losartan potassium in rats are attributed to drug exposure in late gestation and during lactation. |
| **Highly Sensitizing Potential** | A very serious allergic reaction to this drug is rare. |

| IDENTIFICATION OF CRITICAL EFFECTS: | |
|---|---|
| **Sensitive Indicator of an adverse effect seen in non-clinical toxicity data** | No any specific adverse effect seen in non-clinical toxicity data. |
| **Clinical therapeutic and advers effects** | **Usual Adult Dose of Losartan for Diabetic Nephropathy:**<br>**Initial dose:** 50 mg orally once a day.<br>**Maintenance dose:** 25 to 100 mg orally in 1 to 2 divided doses. |

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| | **Usual Adult Dose for Hypertension:**<br>Initial dose: 50 mg orally once a day.<br>**Maintenance dose:** 25 to 100 mg orally in 1 to 2 divided doses.<br><br>**Adverse effects:**<br>• Diarrhea<br>• Stomach pain<br>• muscle cramps<br>• Leg or back pain<br>• Dizziness<br>• Headache<br>• Sleep problems (insomnia)<br>• Tiredness, and<br>• Cold or flu symptoms such as stuffy nose, sneezing, sore throat, fever, and cough |

| | |
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| **NOAEL/LOAEL** | In multiple oral dose (1- and 3-month) toxicity studies with losartan in Sprague-Dawley rats, the NOAEL was 45 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) | 5 | 3 months 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** | |
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| **PDE Calculation** | $\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$<br>$= \frac{45 \text{ (NOAEL) x } 50}{5 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 5}$<br>= 1.8 mg/day |

## 5. REFERENCES:


- https://en.wikipedia.org/wiki/Losartan
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