PERMITTED DAILY EXPOSURE FOR OLMESARTAN MEDOXOMIL

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 Olmesartan Medoxomil 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:

Olmesartan is a medication used to treat high blood pressure, heart failure, and diabetic kidney disease. It is a reasonable initial treatment for high blood pressure. It is taken by mouth. Versions are available as the combination olmesartan/hydrochlorothiazide and olmesartan/amlodipine.

Common side effects include dizziness, headaches, diarrhea, and back pain. Serious side effects may include kidney problems, low blood pressure, and angioedema. Use in pregnancy may harm the baby and use when breastfeeding is not recommended. It is an angiotensin II receptor antagonist and works by blocking the effects of angiotensin II.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Olmesartan Medoxomil is White to light yellowish-white powder or crystalline powder, practically insoluble in water and sparingly soluble in methanol

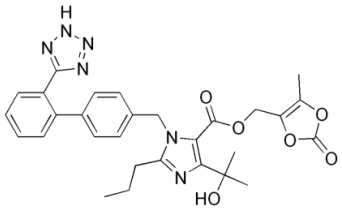
IUPAC name: (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-imidazole-5-carboxylate

Chemical Abstract Services (CAS) Registry Number: 144689-63-4

Molecular Weight: 558.585 g/mol g·mol−1

Chemical Formula: $C_{29}H_{30}N_6O_6$

Molecular Structure:



PERMITTED DAILY EXPOSURE FOR OLMESARTAN MEDOXOMIL

4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Olmesartan Medoxomil inhibits the pressor effect of an angiotensin II infusion in a dose dependent manner at doses of 2.5 to 40 mg. The inhibition was 90% at doses of Olmesartan Medoxomil > 40 mg 24 hours post dose. Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increased after single and repeated administration of Olmesartan Medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg Olmesartan Medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.
Pharmacokinetics data	Absorption: Olmesartan Medoxomil is rapidly and completely bio-activated by ester hydrolysis to Olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of Olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing. The absolute bioavailability of Olmesartan is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of Olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of Olmesartan. Distribution: The volume of distribution of Olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma Olmesartan concentrations well above the range achieved with recommended doses. In rats, Olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats. Metabolism and Excretion: Following the rapid and complete conversion of Olmesartan Medoxomil to Olmesartan during absorption, there is virtually no further metabolism of Olmesartan. Total plasma clearance of Olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.
Acute Toxicity	Olmesartan Medoxomil has low oral acute toxicity in mice, rats and dogs. Doses up to 2000 mg/kg were administered to rats and mice and 1500 mg/kg to dogs with no clinical signs or mortality. Intravenous toxicity studies were conducted with Olmesartan, the active metabolite, in mice and rats. Severe clinical signs occurred at all doses administered in mice

PERMITTED DAILY EXPOSURE FOR OLMESARTAN MEDOXOMIL

SUMMARY OF HAZARD IDENTIFICATION:	
	(≥1700 mg/kg) and rats (≥1400 mg/kg) with lethality in mice at ≥1850 mg/kg and at ≥1550 mg/kg in rats.
Repeated Dose Toxicity (Chronic Toxicity)	Oral repeat dose toxicity studies were conducted in mice, rats and dogs with Olmesartan Medoxomil. Repeat dose (14-day) intravenous studies were conducted with Olmesartan (the active metabolite) in rats and dogs. These studies demonstrated that Olmesartan Medoxomil was well tolerated at doses up to 4000 mg/kg/day in mice (90 days), 1000 mg/kg/day in rats (6 months) and 160 mg/kg/day in dogs (12 months). There were no treatment-related clinical findings at these dose levels. Severe clinic pathological effects associated with uremia necessitated the early necropsy of one dog administered 500 mg/kg (90-day study). Hematological effects (decreased RBC count, hemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time) in rodents, clinical chemistry changes (increase in BUN and creatinine) in rodents and dogs, and histopathological findings in kidneys of rodents and dogs were observed. In kidney, hypertrophy and hyperplasia of the juxtaglomerular apparatus, accompanied by an increase in cytoplasmic granularity are considered to be due to the pharmacological effects of Olmesartan on the Renin-Angiotensin System. At high doses, renal tubular regeneration was observed in rats and dogs and progressive increase in chronic neuropathy was observed in rats. Decreased heart weights, observed in mice and rats were attributed to a decrease in heart muscle load following a reduction in blood pressure. Saline as a water source in rats treated with Olmesartan Medoxomil attenuated/eliminated the observed effect. The findings from studies in rats and dogs where Olmesartan was administered IV for 14 days were consistent with the above-mentioned findings observed after oral administration.
Carcinogenicity	Oncogenicity studies demonstrated that Olmesartan Medoxomil was not carcinogenic when administered at doses up to 2000 mg/kg/day in rats for up to 2 years (equivalent to about 480 times the maximum recommended human dose (MRHD) of 40 mg/day on a mg/m2 basis). A 26-week oncogenicity study conducted in the transgenic mouse strain C57BL/6 TacfBR-[KO] N5 p53(+/-) treated with up to 1000 mg/kg/day (about 120 times the MRHD) Olmesartan Medoxomil revealed no evidence of carcinogenic potential.
In vivo/In vitro Genotoxicity Studies	Both Olmesartan Medoxomil and Olmesartan tested negative in the in vitro Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. Olmesartan Medoxomil tested negative in vivo for mutations in the Muta Mouse intestine and kidney, for clastogenicity in mouse bone marrow (micronucleus test), DNA repair in the UDS assay and DNA fragmentation in the Comet assay at oral doses of up to 2000 mg/kg.

PERMITTED DAILY EXPOSURE FOR OLMESARTAN MEDOXOMIL

SUMMARY OF HAZARD IDENTIFICATION:	
Reproductive/Developmental Toxicity	There was no effect on fertility in rats at doses up to 1000 mg/kg/day (240 times the MRHD) of Olmesartan Medoxomil. No teratogenic effects and no significant effects on the number of corpora lutea, implants and dead/live fetuses were observed in rats at doses up to 1000 mg/kg/day and in rabbits at doses up to 1 mg/kg/day. Perinatal/postnatal toxicity studies in rats demonstrated that a NOAEL for developmental toxicity is 0.3 mg/kg/day of Olmesartan Medoxomil. **Fetal toxicity Pregnancy Category D**: Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Benicar as soon as possible
Highly Sensitizing Potential	Cutaneous side effects to use of valsartan have been reported in literature. Ozturk et al. reported itchy erythematous maculopapular **rashes** all over the body after taking valsartan. **Olmesartan** has also exhibited a similar side effect as that of valsartan (a fellow ARB), an exanthematous drug reaction.

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	**Adult Hypertension dose:** **Starting dose:** 20 mg once daily. **Adverse Effects:** **Serious allergic symptoms include:** • Swelling of your face, lips, throat, or tongue • Low blood pressure (hypotension). Symptoms can include: • Faintness • Dizziness • Liver problems. Symptoms can include: • Nausea • Pain in the right upper part of your stomach • Yellowing of the whites of your eyes and your skin • Itchy skin • Kidney problems. Symptoms can include: • Swelling of your feet, ankles, or hands • Weight gain

NOAEL/LOAEL	The NOAEL after oral administration of Olmesartan Medoxomil were 100 mg/kg/day for male rats (1 year study).

PERMITTED DAILY EXPOSURE FOR OLMESARTAN MEDOXOMIL

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)	1	1 year study in rats.
F4: Severe Toxicity (1-10)	10	Pregnancy D category drug.
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected (The NOAEL after oral administration of Olmesartan Medoxomil were 100 mg/kg/day for male rats.).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{100 (NOAEL) x 50}}{\text{5 x 10 x 1 x 10 x 5}}$ = 2 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Olmesartan
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Olmesartan%20PMe%2020170203.pdf
- https://mri.cts-mrp.eu/Human/Downloads/DE_H_0525_004_PAR.pdf