PERMITTED DAILY EXPOSURE FOR TELMISARTAN

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 Telmisartan 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:

Telmisartan is used to treat high blood pressure, heart failure, and diabetic kidney disease. It is a reasonable initial treatment for high blood pressure.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as Telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that Telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.

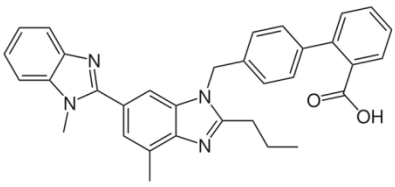
IUPAC name: [1, 1'-Biphenyl]-2-carboxylic acid, 4'-[(1, 4'- dimethyl-2'-propyl [2,6'-bi- 1H-benzimidazol]-1'-yl) methyl]-(CAS)

Chemical Abstract Services (CAS) Registry Number: 144701-48-4

Molecular Weight: 514.63 g/mol

Chemical Formula: $C_{33}H_{30}N_4O_2$

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:	
Pharmacodynamics data	Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT1), with a binding affinity 3000 times greater for AT1 than AT2. In addition to blocking the RAS, Telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD). Telmisartan's activity at the peroxisome proliferator-activated receptor delta (PPAR-δ) receptor has prompted speculation around its potential as a sport doping agent as an alternative to GW 501516.[11] Telmisartan activates PPAR-δ receptors in several tissues. Also, Telmisartan has a PPARγ agonist activity.
Acute Toxicity	In acute oral toxicity studies no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest oral dose tested. The intravenous LD50 in rats was 150-200 mg/kg in males and 200-250 mg/kg in females.
Repeated Dose Toxicity (Chronic Toxicity)	Chronic oral toxicity of Telmisartan was evaluated in studies following administration of doses ≤500 mg/kg for ≤26 weeks in rats, and ≤1 year in dogs. Chronic intravenous toxicity was evaluated in studies of ≤4 weeks at doses ≤20 mg/kg in rats and ≤50 mg/kg in dogs. Repeated dose administration of Telmisartan resulted in marked and long lasting hypotension, hyperplasia of juxtaglomerular apparatus and lesions o the gastrointestinal tract. Further effects were reduced body weight gain, heart weight and red blood cell indices, increased potassium and AST and ALT, the latter in the absence of morphological evidence of toxicity. No effect doses were not identified for decreased erythroid indices, increased BUN and juxtaglomerular hypertrophy/hyperplasia in rats and dogs.
Carcinogenicity	The carcinogenic potential of Telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg and in rats at 3, 15 and 100 mg/kg. Drug administration did not affect survival time in either study and also tumor mortality was not increased. Incidence and time to appearance of palpable masses showed no treatment influence in mice and rats. **No increases were observed in overall tumor incidence, incidence of benign and malignant tumors or tumor multiplicity.**
In vivo/In vitro Genotoxicity Studies	**Telmisartan was not mutagenic** at a concentration range of 10 to 2500 ug/plate in the bacterial reverse mutation assay, with or without metabolic activation. No potential for chromosomal damage was found in the mouse micronucleus test at a dose range of 250 to 1000 mg/kg. No forward mutations at the HPRT locus in V79 cells were induced at a concentration range of 10 to 100 µg/ml, with or without metabolic activation. No chromosomal aberrations were induced in human peripheral lymphocytes in vitro at concentrations ≤100 µg/ml without metabolic activation and concentrations ≤200 µg/ml with metabolic activation.
Reproductive/Developmental Toxicity	In studies on fertility and reproductive performance in male and female rats no effect on mating performance, reproductive organs, or fertility in either sex, or on litter parameters was observed with Telmisartan doses of 5-100 mg/kg. **No Teratogenic or embryotoxic potential in rats was observed at doses ≤50 mg/kg administered from day 7 through day 16 of pregnancy.** However, at toxic dose levels, non-clinical studies indicated

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SUMMARY OF HAZARD IDENTIFICATION:	
	some hazardous potential of Telmisartan to fetal development (increased number of late resorption in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality. Telmisartan was detectable in the placenta, fetus and amniotic fluid of rats after single oral doses of 1 mg/kg.
Highly Sensitizing Potential	No allergic reaction or hypersensitivity develops in normal tissue after repeated exposure to the Telmisartan.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Drugs with direct action on the renin-angiotensin system can cause injury or death to the developing fetus. Stop therapy as soon as possible when pregnancy is detected.
Clinical therapeutic and adverse effects	**Initial dose:** 40 mg orally once a day **Maintenance dose:** 40 to 80 mg orally once a day Side effects are similar to other angiotensin II receptor antagonists and include tachycardia and bradycardia (fast or slow heartbeat, hypotension, (low blood pressure) and edema (swelling of arms, legs, lips, tongue, or throat, the latter leading to breathing problems). Allergic reactions may also occur.

NOAEL/LOAEL	0.1 mg/kg/day NOAEL value selected.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2	For extrapolation from Dogs to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	2	6 month (26 weeks) study 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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{0.1\ (\text{NOAEL}) \times 50}{2 \times 10 \times 2 \times 1 \times 5}$ $= 0.025$ mg/day

5. REFERENCES:

- https://www.boehringer-ingelheim.ca/sites/ca/files/documents/micardispmen.
- https://en.wikipedia.org/wiki/Telmisartan.
- https://www.drugbank.ca/drugs/DB00966.
- https://www.drugs.com/dosage/telmisartan