PERMITTED DAILY EXPOSURE FOR METOPROLOL TARTRATE

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 Metoprolol Tartrate 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:

Metoprolol is a medication of the selective β1 receptor blocker type. It is used to treat high blood pressure, chest pain due to poor blood flow to the heart and a number of conditions involving an abnormally fast heart rate. It is also used to prevent further heart problems after myocardial infarction and to prevent headaches in those with migraines.

Common side effects include trouble sleeping, feeling tired, feeling faint, and abdominal discomfort. Large doses may cause serious toxicity. Risk in pregnancy has not been ruled out. It appears to be safe in breastfeeding. Greater care is required with use in those with liver problems or asthma. Stopping this drug should be done slowly to decrease the risk of further health problems.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

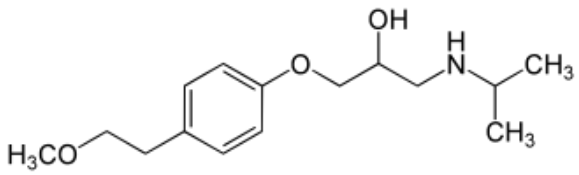
IUPAC name: (RS)-1-[4-(2-Methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol

Chemical Abstract Services (CAS) Registry Number: 51384-51-1

Molecular Weight: 267.369 g·mol−1

Chemical Formula: $C_{15}H_{25}NO_3$

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	Relative beta1 selectivity is demonstrated by the following: (1) In healthy subjects, Lopressor is unable to reverse the beta2-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective (beta1 plus beta2) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, Lopressor reduces FEV1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent beta1-receptor blocking doses. Lopressor has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Animal and human experiments indicate that Lopressor slows the sinus rate and decreases AV nodal conduction. Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta blockade was achieved at approximately 20 minutes. Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1. There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration. In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of Lopressor caused a reduction in heart rate, systolic blood pressure and cardiac output. Stroke volume, diastolic blood pressure and pulmonary artery end diastolic pressure remained unchanged. In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50-400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of Metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.
Pharmacokinetics data	**Absorption:** The estimated oral bioavailability of immediate release Metoprolol is about 50% because of pre-systemic metabolism which is saturable leading to non-proportionate increase in the exposure with increased dose. **Distribution:** Metoprolol is extensively distributed with a reported volume of distribution of 3.2 to 5.6 L/kg. About 10% of Metoprolol in plasma is bound to serum albumin. Metoprolol is known to cross the placenta and is found in breast milk. Metoprolol is also known to cross

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the blood brain barrier following oral administration and CSF concentrations close to that observed in plasma have been reported. Metoprolol is not a significant P-glycoprotein substrate

Metabolism: Lopressor is primarily metabolized by CYP2D6. Metoprolol is a racemic mixture of R- and S- enantiomers, and when administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. CYP2D6 is absent (poor metabolizers) in about 8% of Caucasians and about 2% of most other populations. Poor CYP2D6 metabolizers exhibit severalfold higher plasma concentrations of Lopressor than extensive metabolizers with normal CYP2D6 activity thereby decreasing Lopressor's cardioselectivity.

Elimination: Elimination of Lopressor is mainly by biotransformation in the liver. The mean elimination half-life of Metoprolol is 3 to 4 hours; in poor CYP2D6 metabolizers the half-life may be 7 to 9 hours. Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolizers), less than 5% of an oral dose and less than 10% of an intravenous dose are excreted as unchanged drug in the urine. In poor metabolizers, up to 30% or 40% of oral or intravenous doses, respectively, may be excreted unchanged; the rest is excreted by the kidneys as metabolites that appear to have no beta blocking activity. The renal clearance of the stereoisomers does not exhibit stereo-selectivity in renal excretion.

Acute Toxicity

Case 1: In LD50 determination studies, the toxic symptoms in rats included: sedation, piloerection, ataxia, irritation, spasm and lacrimation. Rats were unconscious before death, which occurred within 5-10 min after intravenous injection and 6-20 hr after oral administration. In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection. No symptoms of toxicity were detectable 24 h after administration in surviving animals.

Species	Sex	Route	Solutions	LD_{50} (mg/kg)
Mouse	M	i.v	1%	69.4±5.1
Mouse	F	i.v	1%	79.9±4.5
Mouse	M	p.o.	23%	2460±210
Mouse	F	p.o.	25%	2300±200
Rat	M	i.v.	5%	71.9±4.1
Rat	F	i.v.	5%	74.3±4.4
Rat	M	p.o.	50%	4670±1210
Rat	F	p.o.	50%	3470±580

Case 2: Acute toxicity of Metoprolol (LD 50) was investigated in mice and rats by gavage or by intravenous (i.v.) injection. The animals were observed for 14 days. The toxic symptoms seen in rats after administration of Metoprolol tartrate included sedation, piloerection, ataxia, irritation, spasm, lacrimation, red discharge around the eyes and

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SUMMARY OF HAZARD IDENTIFICATION:

nostrils. Rats were unconscious before death, which occurred within 5-10 minutes after i.v. and 6-20 hours after oral administration. In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection. There was no toxicity detected 24 hours after administration of metoprolol in surviving animals. The calculated LD50 values, expressed in mg/kg body weight, are given in Table 6 [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014.

Species	Sex	Route	Solutions	LD_{50} (mg/kg)
Mouse	M	i.v	1%	69.4±5.1
Mouse	F	i.v	1%	79.9±4.5
Mouse	M	p.o.	23%	2460±210
Mouse	F	p.o.	25%	2300±200
Rat	M	i.v.	5%	71.9±4.1
Rat	F	i.v.	5%	74.3±4.4
Rat	M	p.o.	50%	4670±1210
Rat	F	p.o.	50%	3470±580

In acute toxicity studies conducted with metoprolol succinate salt, calculated LD50 in mice by oral route was 870 (710-1000) mg/kg and in rats was 2000 (1700-2600) mg/kg [NDA 019962, 1991].

Repeated Dose Toxicity (Chronic Toxicity)

In Chronic toxicity studies in rats & dogs administered Metoprolol orally, test compound related findings were limited to the dog with the observation of bradycardia, increase PR intervals & QT prolongation in a 6 month repeated dose toxicity study at dosage of 0, 5, 20 & 40 mg/kg twice a day. In this study in the dog the high dosage of 40 mg/kg twice a day was increased to 50 mg/kg twice a day and after 3 month the intermediate dosage was increased to 30 mg/kg twice a day and the high dosage was increased to 80 mg/kg twice a day. The death of 2 dogs receiving the highest dosage was reported in a 1 year repeated dose toxicity study where animals received 0, 10 & 60 mg/kg/day on days 3 to 8, 90 mg/kg/day on days 9 to 22 & 105 mg/kg/day for the rest of the study.

In the rat: 5-week repeated dose toxicity study

Male and female SD rats (10 animals/sex/dose group) received Metoprolol hydrochloride by gavage once daily for 5 weeks at dosages of 10, 50 and 100 mg/kg increased after 14 days to 200 mg/kg for the high dose. No adverse effects were observed. Slight increase in the hematocrit and slight decrease in the blood glucose concentration were noticed among the females in the high dose. **The NOAEL was 200 mg/kg in both genders** [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975]. 6-month repeated dose toxicity study: Male and female SD rats (15 animals/sex/dose group) were given Metoprolol tartrate by gavage once daily for 6 months at dosages of 10, 100 and 200 mg/kg initially and increased from 200 to 250 mg/kg after 13 weeks of dosage. The NOAEL in this study was the highest dosage tested of 250 mg/kg in

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SUMMARY OF HAZARD IDENTIFICATION:	
	both genders [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975]. In the dog: 1) By oral administration (capsule): MTD: The MTD of Metoprolol in the dog was measured in several studies. One male and one female Beagle dog received Metoprolol hydrochloride orally, beginning with the dose of 40 mg/kg for three days, followed by increases in dose of 20 mg/kg every day until the dosage level of 160 mg/kg was reached. The dose of 140 mg/kg was given for six days. At 0.5 to 3 hours after administration dose-dependence disturbance of balance, increased abdominal muscular tone, mydriasis and hyperemia in mucous membranes were noted. One of the dogs was found dead 45 minutes after dose administration on Day 16 at the dosage of 160 mg/kg. The other dog was treated for a further week and reached the dosage level of 160 mg/kg. In another study, Metoprolol tartrate was administered orally to female dogs beginning at the dosage of 20 mg/kg twice a day with an increase every fifth day of 20 mg/kg twice a day up to the dosage level of 120 mg/kg twice a day. Male dogs were given 80 mg/kg twice a day one day and two days later a single dose at 100 mg/kg. In the females there was a dose dependent increase in severity of vomiting and increased salivation after administration of the test compound. At dosages 60 mg/kg twice a day incoordination, tremor and ataxia occurred at 0.5-4 hours after administration. One of the female dogs was found dead on the fifth day at the dose level 120 mg/kg twice a day and the study was discontinued. In the male dogs, vomiting, loss of balance and severe dyspnea were observed beginning at 60-90 minutes after administration. The dog became unconscious and died 160 minutes after administration without convulsions occurred [Product Monograph of TevaMetoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975]. 1-month repeated dose toxicity study: Male and female dogs (1 animal/sex/dose group) received Metoprolol hydrochloride orally at the daily dosages of 5, 20 and 40 mg/kg for 1 month. The ECG showed a prolonged PR-interval in the treated dogs 60 minutes after administration of Metoprolol. The effect did not seem to be dose-dependent and was of similar magnitude at the beginning and at the end of the study. The prolongation of the PR-interval was reversible and was considered related to the pharmacological effect of Metoprolol. The clinical chemistry and pathology were unremarkable [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975] The NOAEL in this study was the highest dose tested of 40 mg/kg/day. 3-month repeated dose toxicity study: Male and female dogs (3 animals/sex/dose group) received Metoprolol succinate orally at the dosage of 5, 20 and 40 mg/kg/twice a day and Metoprolol tartrate orally at the dosage of 40 mg/kg/twice a day for 3 months. One animal died due to circulatory failure and pulmonary edema on Day 2 of Metoprolol tartrate administration. There was a tendency to prolongation of the P-R interval in all 80 mg/kg/day groups, whether receiving tartrate or succinate, and one animal administered Metoprolol succinate exhibited a second degree A-V

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	block 4 hours after the first dose and 1 hour after the second dose on Day 4 of the study [NDA 019962, 1991]. 6-month repeated dose toxicity study: Male and female dogs (3 animals/sex/dose group), received orally twice daily administration of 5, 20 and 40 mg/kg Metoprolol for 6 months. After weeks the high dose was increased to 50 mg/kg twice daily. After 3 months the mid-dosage was increased to 30 mg/kg twice daily and the high dosage was increased to 80 mg/kg twice daily. There was a slight bradycardia during the first few hours after administration and increased PR and QT-intervals that were related to the pharmacological effects of Metoprolol. No other remarkable effects were observed [Product Monograph of Teva-Metoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975]. 1-year repeated dose toxicity study: Male and female Beagle dogs (6 animals/sex/dose group) received metoprolol orally at the dosages of 0, 10 (low dose) and 60 (mid-dose) mg/kg/day for 1 year. The high dose group received 120 mg/kg on Day 1, 60 mg/kg on Days 3 to 8, 90 mg/kg/day on Days 9 to 22 and 105 mg/kg/day for the rest of the study. Two dogs in this group died on Day 1. No other signs of toxicity were observed in all dose treated groups [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014]. 2) By intravenous administration in the dog: Male and female dogs (1 animal/sex/dose group) received intravenously metoprolol hydrochloride at the dosages of 0.5 and 5 mg/kg/day for 2 weeks. A non dose-dependent prolonged PR-interval was observed 5 minutes after administration that was reversible [Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014].
Carcinogenicity	Metoprolol was administered to 3 groups of 60 male and 60 female Charles River Sprague Dawley rats at dietary levels of 50, 200 and 800 mg/kg per day for 78 weeks. A fourth group served as the positive control (2-AAF) and the fifth was the negative control group. The incidence of nodules and masses observed at necropsy were comparable between the treated and control groups. The only histopathological changes noted were an increased incidence of impaction of pulmonary alveoli by septal cells in all the treated animals and an increase in biliary hyperplasia in the high and intermediate Metoprolol-treated groups. The strain of rats was susceptible to the known carcinogen 2-AAF; a statistically higher incidence of neoplasms, primarily hepatomas, was present. A similar study in Swiss albino mice at doses of 75, 150 and 750 mg/kg/day for 78 weeks showed no excess tumors. The conclusion was that Metoprolol did not increase the incidence of neoplasms in rats and mice.
In vivo/In vitro Genotoxicity Studies	There was no evidence of Genotoxicity of Metoprolol in the following tests: a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei [Prescribing Information on Toprol-XL (Metoprolol succinate) tablet, Astra-Zeneca, 2014].
Reproductive/Developmental Toxicity	**Rat teratology:** Metoprolol at dosages of 10, 50 and 200 mg/kg was administered orally to groups of 20 pregnant SD rats on days 6-15 of gestation. Treatment with Metoprolol did not adversely affect any of the parameters studied [Borg, 1975].

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:	
	Rabbit teratology: Metoprolol at dosages of 5, 12.5 and 25 mg/kg was administered orally to groups of 20 pregnant New Zealand White rabbits on days 6-18 of gestation. Parameters studied were not significantly affected, although litter size was lower and fetal loss higher in the high dose group. The incidence of fetal abnormality was unaffected by treatment [Bodin, 1975]. **Peri-and post-natal development studies:** Metoprolol at dosages of 10, 50 and 200 mg/kg was administered orally to groups of 50 SD rats from day 15 of gestation, through lactation to 21 days postpartum. Parameters studied in litter and parent animals were not adversely affected [Bodin, 1975]. **Fertility studies:** Metoprolol at dosages of 50 and 500 mg/kg was administered orally to groups of 10 male and 20 female Charles River CD strain rats. Males were treated for 63 days prior to mating and during the mating period. The females were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days post-partum, with an interim sacrifice at day 13 of gestation. Survival, growth and fertility of male and female rats were unaffected by the treatment. The significant findings in this study were slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day, a higher frequency of stillbirths and reduced mean number of viable newborns in the high dose group, postnatal survival of pup in the drug-treated groups showed a dose-related reduction compared to controls [Product Monograph of Teva-Metoprolol (Metoprolol tartrate) tablets, Teva, 2014; Bodin, 1975].
Highly Sensitizing Potential	The most common side effects with **Metoprolol** are low blood pressure; slow heart rate; dizziness; fatigue; depression; itchy **skin**; rash; and diarrhea.

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	• **For Acute heart attack or heart failure:**
	  ○ For oral dosage form (extended-release tablets):
	  ▪ Adults-25 mg once a day for 2 weeks.
	  ○ For oral dosage form (tablets):
	  ▪ Adults-50 mg every 6 hours for 2 days. Then, 100 mg 2 times a day.
	• **For Chest pain:**
	  ○ For oral dosage form (extended-release tablets):
	  ▪ Adults-100 mg once a day.
	  ○ For oral dosage form (tablets):
	  ▪ Adults-100 mg per day, given in two divided doses.
	• **For High blood pressure:**
	  ○ For oral dosage form (extended-release tablets):
	  ▪ Adults-25 to 100 mg once a day.
	  ○ For oral dosage form (tablets):
	  ▪ Adults-100 mg per day, given as a single dose or in divided

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	doses. **Adverse effects**: Signs of an allergic reaction to Metoprolol: Hives; difficulty breathing; swelling of your face, lips, tongue, or throat.
NOAEL/LOAEL	The NOAEL was 200 mg/kg in both genders (5 week studies).

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)	10	Short duration study in rodent (5 weeks).
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 [The NOAEL was 200 mg/kg in both genders (5 week studies].
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{200 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 4 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Metoprolol
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017963s068lbl.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210428Orig1s000PharmR.pdf
- https://www.mayoclinic.org/drugs-supplements/metoprolol-oral-route/proper-use/drg-20071141