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APPLICATION NUMBER:

210428Orig1s000

NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 210428
Supporting document/s: IND 127963, NDA 019962
Applicant's letter date: June 12, 2017
CDER stamp date: March 30, 2017
Product: Metoprolol Succinate Extended Release Capsules at
25, 50, 100 and 200 mg
Indication: Hypertension, angina pectoris, heart failure (b) (4)
[REDACTED]
[REDACTED]
Applicant: Sun Pharmaceuticals Industries Limited
Review Division: DCRP
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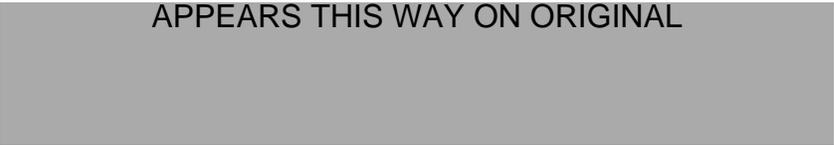
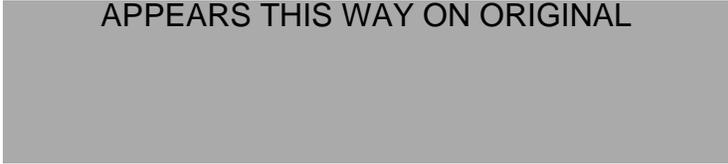


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1 Executive Summary:

1.1 Introduction:

The sponsor Sun Pharmaceuticals Industries Limited proposes the development of a capsule form of TOPROL-XL® tablets. This capsule form will be available at the nominal dosages of 25, 50, 100, and 200 mg similar to TOPROL-XL® tablets and will have the same indications except for the exclusion with the capsule of the treatment of NYHA Class II heart failure with 12.5 mg once daily in patients with more severe heart failure (b) (4)

The capsule form will allow the sprinkling of the active compound over food for patients who have difficulty swallowing a tablet.

The sponsor is using the 505(b)2 NDA pathway for approval and therefore is submitting bioequivalence data to the Reference Listed Drug (RLD) TOPROL-XL® *Tablets* at 25 mg, 50 mg, 100 mg and 200 mg (manufactured by ARALEZ PHARMACEUTICALS) first approved in 1992 (NDA 019962). Similarly, the demonstration of the safety of the capsule is based on the FDA findings for the innovator compound metoprolol succinate and generics and on literature articles citing metoprolol and dated from 2014 (date of the latest RLD labeling update) to present.

1.2 Brief Discussion of Nonclinical Findings:

Overall, the extensive review of the updated non-clinical literature revealed that there are no new safety issues. Furthermore, systemic effects of metoprolol have already been well characterized and long clinical experience support the safety of metoprolol at judicious doses.

1.3.1 Approvability:

No new safety findings of concern were found and this product is approvable from the pre-clinical development aspect. Furthermore an extensive clinical experience in adults and children ≥ 6 years old with metoprolol is available.

1.3.2 Additional Non Clinical Recommendations:

There are no additional non clinical recommendations.

1.3.3 Labeling:

Below is the new sponsor’s proposal for Section 8 of the label. (b) (4)

This reviewer agrees with the pre-clinical information conveyed with this new labeling Section 8 in conformity with the Pregnancy and Lactation Labeling Rule (PLLR):

Original section 8 for the RLD:

8.1 Pregnancy

(b) (4)

(b) (4)

(b) (4)



2 Drug Information:

2.1 Drug:

CAS Registry Number:
98418-47-4

Generic Name:
Metoprolol succinate

Code Name:
N/A

Chemical Name:

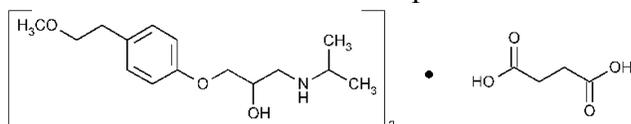
(b) (4)

2)(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanolsuccinate (2:1)(salt).

Molecular Formula/Molecular Weight:

C₁₅H₂₅NO₃)₂·C₄H₆O₄/652.81

Structure or Biochemical Description:



Pharmacologic Class:

Beta1-adrenoceptor blocking agent.

2.2 Relevant INDs, NDAs, BLAs and DMFs:

NDA 019962; IND127963

1) NDA 019962; Metoprolol Succinate Extended-Release *Capsules* at 25 mg, 50 mg, 100 mg and 200 mg is bioequivalent to the Reference Listed Drug (RLD) TOPROL-XL® *Tablets* at 25 mg, 50 mg, 100 mg and 200 mg (ARALEZ PHARMACEUTICALS) first approved in 1992.

2) IND 127963: Metoprolol Succinate Extended-Release *Capsules* 25 mg, 50 mg, 100 mg and 200 mg submitted by the sponsor Sun Pharmaceuticals Industries Limited on June 08, 2016.

2.3 Drug Formulation:

The drug product is administered orally once a day. The recommended maximum daily dose of Metoprolol Succinate Extended -Release Capsules is 400 mg in one dose. The content of the capsule can be sprinkled over food.

2.4 Comments on Novel Excipients:

The inactive ingredients in the proposed generic are ethyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 6000, sugar spheres (corn starch and sucrose), talc and triethyl citrate. The capsule shell and imprinting ink has the following composition: ferric oxide yellow (25 mg, 50 mg and 200 mg), ferrosferric oxide, gelatin, potassium hydroxide, propylene glycol, shellac and titanium dioxide. These inactive ingredients are different from the RLD which contains instead silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, and paraffin.

The sponsor provided justification that all excipients are safe to use for oral consumption in adults and children at the maximum dosages for the proposed indications.

[NDA210428 excipients safety.pdf](#)

2.5 Comments on Impurities/Degradants of Concern:

The acceptance criteria for all impurities/degradants in drug substance and product are in line with the USP monograph for Metoprolol Succinate, DMF Holder's specifications and are based on the US FDA's Guidance for Industry, "ANDAs: Impurities in Drug Substance and Drug Product". Therefore there are no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen:

Sun Pharma intends to develop an Extended-Release Capsule formulation of Metoprolol Succinate 25 mg, 50 mg, 100 mg and 200 mg bioequivalent to existing RLD TOPROL-XL 25 mg, 50 mg, 100 mg and 200 mg tablets that may be administered as a sprinkle over soft foods. Sun Pharma also intends to perform studies to support nasogastric tube administration of the pellets to adults and children above 6 years of age, population needing administration through nasogastric tubes. The proposed drug product represents the same uses, strengths and route of administration (additionally, through nasogastric tube administration); differing in dosage form (from Tablets to Capsules) from the RLD. The sprinkle based formulation bioequivalent to Toprol XL can be used for long term care of patients having dysphagia. The maximum daily dose of Metoprolol Succinate Extended-Release Capsule is 400 mg.

Currently Approved Dosage Regimen of Metoprolol Succinate Extended- Release Tablets (extracted from the latest label for TOPROL-XL dated 2014 in NDA 019962):

Hypertension:

Adults:

The usual initial dosage is 25 to 100 mg daily in a single dose. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Pediatric hypertensive patient \geq 6 years of age:

The recommended starting dose of Metoprolol Succinate Extended- Release Tablets is 1.0 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients. Metoprolol Succinate Extended-Release Tablets are not recommended in pediatric patients <6 years of age.

Angina Pectoris:

Individualize the dosage of Metoprolol Succinate Extended-Release Tablets. The usual initial dosage is 100 mg daily, given in a single dose. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dosage gradually over a period of 1-2 weeks.

Heart Failure:

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Metoprolol Succinate Extended-Release Tablets, stabilize the dose of other heart failure drug therapy. The recommended starting dose is 25 mg once daily for two weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg.

2.7 Regulatory Background

Sun Pharmaceuticals Industries Limited is pursuing a marketing application for Metoprolol Succinate Extended-Release Capsules at 25 mg, 50 mg, 100 mg and 200 mg via the 505 (b)(2)NDA regulatory pathway with a modified indication. The new indication will exclude treatment of severe heart failure (b) (4)

The approval of this product is based on prior FDA finding of safety and effectiveness for the reference listed drug (RLD) in NDA 019962 first approved in 1992. The RLD is Metoprolol Succinate Extended-Release Tablets (TOPROL-XL) at 25 mg, 50 mg, 100 mg and 200 mg. The sponsor supplemented the FDA findings for the RLD with findings on metoprolol succinate extracted from the published literature covering the years 2014 to present.

3 Studies Submitted:

The efficacy and safety of the reference product has been proved in clinical trials and the test product is being developed as a new pharmaceutical formulation alternative to the RLD (capsule versus tablet).

The innovator (Astra Zeneca) produced a package of studies in NDA 019962 approved by FDA in 1992 including non-clinical pharmacology and pharmacokinetics studies, single dose toxicity study in rats and mice, repeat dose toxicity studies (5 weeks and 6 months oral in rats and 2 weeks (i.v. route), 1 month, 6 months and 1 year oral in dogs), *in vivo* and *in vitro* genotoxicity studies, 2-year carcinogenicity studies in rats and mice and reproductive toxicity studies (fertility, early embryonic development study and a peri/postnatal studies).

In addition, an extensive clinical experience in adults and children ≥ 6 years old with metoprolol is available. Therefore no new non clinical studies were provided by Sun Pharmaceutical Industries Limited for approval of NDA 210428. This is a 505(b)2 NDA which relies on public knowledge for the RLD and the review of the recent scientific literature on metoprolol succinate.

3.1 Studies Reviewed:

NA

3.2 Studies Not Reviewed:

NA

3.3 Previous Reviews Referenced:

NA

4 Pharmacology:

1) *Summary based on previous findings for the RLD:*

Effect on the Cardiovascular System:

- Metoprolol produced dose-dependent reductions in heart rate and contractile force responses to sympathetic nerve stimulation in the anesthetized cat. The ED₅₀ value for blockade of the chronotropic response to nerve stimulation was approximately 7 times less than that for isoproterenol stimulation.

- Metoprolol reduced the heart rate in conscious dogs at rest and during exercise. With the exception of PR interval prolongation, ECG complexes were not changed.
- In anesthetized cats, intravenous doses up to 2.0 mg/kg did not significantly influence the pressor response to intravenous epinephrine.
- In anesthetized cats, intravenously-administered metoprolol antagonized the hind limb vasodilating response to intra-arterial isoproterenol in much higher doses (ED₅₀: 5 mg/kg) than required to block the increase in chronotropic response (ED₅₀ 0.4 mg/kg) or increase in contractile force (ED₅₀: 0.2 mg/kg).
- Studies in reserpinized cats showed that metoprolol was devoid of β -receptor stimulating (intrinsic) activity. In cumulative doses up to 0.85 mg/kg, the drug did not significantly influence heart rate or contractile force.

Other Effects:

- Metoprolol showed a negligible local anesthetic effect on the isolated sciatic nerve of the frog and in the intra-cutaneous wheal test in guinea pigs. This would contrast with propranolol which has marked local anesthetic activity, about 50% of that of lidocaine.
- The cardio-stimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg metoprolol in the anesthetized cat.
- At this dosage metoprolol was found to be devoid of anticholinergic, ganglionic blocking, antihistaminic and alpha-receptor blocking properties in cats.
- Metoprolol inhibited the increase in plasma renin activity induced by furosemide.
- The effects of metoprolol on isoproterenol-stimulated metabolic effects showed inhibition of the increase in liberation of glycerol, glucose, insulin and free fatty acids.

2) Summary of new pharmacology findings for metoprolol in the past 5 years (extracted from the literature):

The focus is on any new safety issues arising from on-target β -blockade by metoprolol in heart failure, asthma, hypertension and arrhythmia and reproductive toxicity (see below in the appropriate section). The totality of the new information is summarized in the attached hyperlink:

[NDA 210428 new pharmacology.pdf](#)

The sponsor provided thirty four citations about the pharmacological effects of metoprolol observed in various animal models. These studies forecast either efficacy or afford mechanistic insight into the effect of β -blockade by metoprolol in heart failure, arrhythmia or hypertension. Overall, the extensive review of non-clinical literature forecast no new safety issues, which could be of concern, pertaining to the use of metoprolol in CV disease. . Furthermore, systemic effects of metoprolol have already been well characterized and long clinical experience also provides enough evidence to support the safety of metoprolol at judicious doses. Below is a brief overview of the salient recent findings extracted from these articles.

- Metoprolol is shown to be a biased ligand that selectively activates a G protein-independent and GRK5/ β -arrestin2-dependent signaling pathways which induced a fibrotic response *in vitro* on isolated cardiac cells from mice after long term administration (30 mg/kg/day orally twice a day for 3 months) (Nakaya, 2012).

- One study in the dog with metoprolol (5 mg/kg/day i.v. continuously for 12 weeks) showed that the test compound protected against chronic obstructive sleep apnea (OSA)-induced cardiac apoptosis and fibrosis in left ventricular myocytes *in vivo* (Li, 2015).
- An experiment in the Duchenne Muscular Dystrophy (mdx) mouse showed that treatment with metoprolol at an early stage in the development of the cardiomyopathy in this disease model can lead to worsening right ventricular function. Metoprolol administration had no effect on the increased myocardial calcium influx in this model (Blain, 2013). Mice received 2.5 mg/kg/day orally beginning at 16 weeks of age and continued for 8 weeks when cardiac function was assessed.
- Metoprolol (4 mg/kg administered 90 minutes before emotional stress by immobilization (IMO)) could attenuate the increases in systemic blood pressure and heart rate during IMO. However it could not prevent (IMO)-induced left ventricular systolic dysfunction in a rat model of emotional stress-induced acute cardiac dysfunction (Ishikura, 2012).
- Based on the findings from *in vitro* culture of cardiac progenitor cells (CPCs) from mice the beneficial effects of β 1-adrenergic blockade (by metoprolol) in the failing heart may also include potentiation of cardiac progenitor cell (CPC) expansion and survival by preventing their differentiation (Khan, 2013).
- The results from an experiment in rats (Su, 2013) suggested that the inhibition of apoptosis can be a potential therapeutic strategy for the treatment of coronary micro-embolization (CME). Three bolus injections of metoprolol (2.5 mg/kg) were given at approximately 5-minute intervals at 30 minutes before CME induction. The metoprolol cohort showed significantly improved cardiac function assessed by echocardiography, and associated with decreased apoptosis and activated caspase 3.
- Zhang (2013) reported that metoprolol (2 mg/day orally for 7 days starting 1 day before coronary artery ligation) inhibited expression of the proto-oncogene c-fos after myocardial infarction. Metoprolol administration also decreased infarct size.
- The long-term exposure to fine particulate air pollution ($PM_{\leq 2.5}$ μ m) is associated with acute myocardial infarction (AMI). Experiments in a rat model of AMI exposed to fine particulate air pollution (Gao, 2014) showed that the combination of metoprolol (20 mg/kg b.i.d., orally) and the β 2-adrenoreceptor agonist terbutaline improved cardiac hemodynamic function and remodeling in this model.
- Wu (2012) demonstrated that early treatment of rats with metoprolol (2.5 mg/kg i.v. bolus injections x3 every 5 minutes starting 30 minutes after AMI induction, then 24 hours later 50 mg/kg b.i.d. orally for 4 weeks) could improve heart function and inhibit left ventricular remodeling after left coronary artery ligation-induced AMI. The mechanism seemed to be linked to the ability of metoprolol to down-regulate the pro-inflammatory cytokines IL-1 beta, IL-6, and TNF-alpha and to up-regulate the anti-inflammatory cytokine IL-10 in cardiac myocytes.

- The results from a rat experiment (Babick, 2013) suggested that the partial improvement of cardiac performance by metoprolol (50 mg/kg/day orally for 8 weeks) at advanced stages of heart failure (12-week infarcted heart) may be due to partial reversal of changes in sarcoplasmic reticular Ca^{2+} -pump function whereas partial to complete reversal of cardiac remodeling may be due to a partial reduction in the elevated levels of plasma catecholamines.

- Consistent with the efficacy of β_1 adrenoreceptor blockade in heart failure, authors concluded from the results of a rabbit experiment (Galougahi, 2013) that the PKA-dependent Na^+ - K^+ pump inhibition should act in synergy with other mechanisms to increase cardiac contractility with β_1 adrenergic stimulation in the normal heart while pump stimulation induced by β_1 adrenoreceptor antagonists should reduce myocyte Na^+ overload. In this study rabbits received 25-50 mg/kg/day metoprolol orally for 3, 7 or 10 days and ventricular myocytes were studied *ex vivo*. Authors showed that the reduction in PKA activity by β_1 adrenergic blockade *in vivo* stimulated the Na^+ - K^+ pump by reducing glutathionylation of one of its subunits, a reversible oxidative modification that inhibits pump activity, and that the Na^+ - K^+ pump stimulation induced by β_1 adrenergic blockade *in vivo* was reversed by activation of PKA-dependent signaling in isolated cardiac myocytes studied *ex vivo*. They concluded that the inhibition of the myocyte Na^+ - K^+ pump mediated by PKA- and redox-dependent signaling pathways and downstream glutathionylation of a subunit of the Na^+ - K^+ pump was readily reconciled with the effects of PKA on contractility in normal heart and efficacy of β_1 adrenergic blockade in heart failure.

- An investigation of the effect of the expression level of myocardial β_1 -adrenergic receptor beta 1 (ADRB1) in spontaneously hypertensive rats (SHR) (Liu, 2013), showed that SHRs with a higher expression level of myocardial ADRB1 had achieved a lower blood pressures e under metoprolol. The authors concluded that the variable expression level of myocardial ADRB1 in patients with essential hypertension could account for inter-individual differences in treatment response.

- Studies with ApoE^{-/-} mice receiving metoprolol 2.5 mg/kg/hour via osmotic minipumps for 11 weeks (Ulleryd, 2014) showed that the treatment significantly reduced atherosclerotic plaque areas in thoracic aorta. Metoprolol also decreased the serum levels of the pro-inflammatory cytokine TNF-alpha, the chemokine CXCL1, and the macrophage numbers in the plaques. Authors concluded that metoprolol has anti-inflammatory properties.

-The results from an experiment conducted in rats suggest that metoprolol (50 mg/kg orally administered 1 day before wounding and then daily during healing) delayed wound healing (Raut, 2012). In this model, metoprolol and propranolol decreased skin tensile strength, re-epithelialization, hydroxyproline content, and increased subcutaneous inflammatory infiltrates. Reviewer' comment: These results contradict the previous findings of the anti-inflammatory properties of metoprolol in an atherosclerosis mouse model. The properties of metoprolol might depend on the model.

- In a model of long-lasting atrial fibrillations in mice (Suita, 2015) induced by trans-esophageal atrial burst pacing and intraperitoneal norepinephrine injection, metoprolol (2 mg/kg i.p. 45 minutes before the injection of norepinephrine) significantly inhibited the norepinephrine-

induced sarcoplasmic reticulum Ca²⁺ leak and the release of calcium in the atrial myocytes. The authors concluded that the β 1-adrenergic receptor may play an important role in atrial fibrillation.

5 Pharmacokinetics/ADME

Summary based on previous findings for the RLD:

- The maximum concentration in plasma after oral administration of the drug in an aqueous solution is reached within 2 hours in all the species studied (Table).
- After oral administration metoprolol is to a certain extent metabolized in the first liver passage.
- The bioavailability is about 50 % at therapeutic oral dose levels.
- Metoprolol is extensively distributed to extravascular tissues including the brain.
- Metoprolol is weakly bound only to serum proteins (~12% in man).
- Metoprolol is eliminated from the body by biotransformation and excretion in the urine mainly as metabolites with a half-life in rat < cat < dog and man.
- The main urinary metabolites in man, the dog and the rat are formed by oxidative deamination, O-dealkylation with subsequent oxidation and by aliphatic hydroxylation. The main metabolite is an amino acid in the species studied. In man, 85 % of the total amount of metabolites in urine could be accounted for. One of the metabolites, hydroxylated metoprolol, and an intermediate to the main metabolite are beta-blockers with the same pharmacological profile as the parent drug but less potent. The acute toxicity in the mouse of the metabolites was lower than for metoprolol.

Table 2. Some pharmacokinetic properties of metoprolol.

Species	t _{max} h	V _d (β) l/kg	t _{1/2} (β) h	C _p (20 %) * μg/ml
Rat	0.5	6.3	0.6	—
Cat**	—	5.5	1.3	—
Dog	0.5—1.5	3.1	1.6	0.03
Man	1—2	5.6	3—4	0.10

* C_p (20 %) = plasma concentration at 20 % reduction of exercise tachycardia

** Anaesthetized

- Metoprolol induces cardiac β -blockade after intravenous administration in dogs. The effect of Metoprolol on tachycardia is linearly related to the logarithm of the plasma concentration of the intact drug in dogs. The concentration levels for significant β -blockade in the conscious dog and in man are within the same range. The effect on the exercise heart rate declines at a constant rate in the conscious dog and in man after intravenous and oral dose. The duration of action of the drug increases with the magnitude of the dose due to the linear decline of the effect with time. The effect on exercise tachycardia is reduced to 50 % of its maximum in about 4 hours in conscious dogs at dose 1 mg/kg (i.v.) with an elimination half-life of about 1.5 hours.

6 General Toxicology

Summary based on previous findings for the RLD:

Acute toxicity:

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 h 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	male	i.v.	1%	69.4 ± 5.1
mouse	female	i.v.	1%	79.9 ± 4.5
mouse	male	p.o.	23%	2460 ± 210
mouse	female	p.o.	25%	2300 ± 200
rat	male	i.v.	5%	71.9 ± 4.1
rat	female	i.v.	5%	74.3 ± 4.4
rat	male	p.o.	50%	4670 ± 1210
rat	female	p.o.	50%	3470 ± 580

Subacute toxicity:

In sub-acute toxicity studies in rats and dogs, metoprolol-related toxicity findings were found in several dog studies. After oral administration in the dog at the dosages of 40 mg/kg three times a day, increased by 20 mg/kg/day to 140 mg/kg/day for 6 days to 160 mg/kg/day, disturbance of balance, increased abdominal muscular tone, mydriasis, hyperemia of mucous membranes and one death at 140 mg/kg/day were observed. After oral administration in the dog at the dosage of 80 mg/kg twice a day for one day and followed 2 days later by a single dose of 100 mg/kg, disturbance of balance, vomiting, prostration, dyspnea, loss of consciousness, and death happened after treatment on Day 3. After oral administration in the dog at the dosages of 20 mg/kg twice a day increased every 5 days by 20 mg/kg twice a day up to 120 mg/kg twice a day for 4 weeks, vomiting, increased salivation, tremors, ataxia, and death of 1 animal receiving the highest dose were observed. After intravenous administration in the dog, prolonged PR intervals were observed in a study where animals received 0, 0.5, and 5 mg/kg/day for 2 weeks.

Subacute Toxicity in Animals

Species	Strain	Sex		No. of Groups	No. of Animals/Group	Dose mg/kg/day	Route	Duration of Study	Toxic Effects
		M	F						
Rats	Sprague-Dawley	40	40	4	10M 10F	Saline, 10, 50, 100 mg/kg/day (after 14 days, high dose incr. to 200 mg/kg/day)	p.o.	5 weeks	Slight incr in hematocrit & slight decr in blood sugar in high dose females.
Dogs	Beagle	1	1	1	1M 1F	40 mg/kg x 3 days, incr. by 20 mg/kg/day to 140 mg/kg x 6 days to 160 mg/kg/day.	p.o.	3 weeks	Disturbance of balance, incr abdominal muscular tone, mydriasis, hyperemia in visible mucosa membranes. One dog died at dose level of 140 mg/kg/day.
Dogs	Beagle	1	2	2	1M 2F	80 mg/kg b.i.d./one day; 2 days later, single dose of 100 mg/kg 20 mg/kg b.i.d., incr. every 5 days by 20 mg/kg b.i.d. up to 120 mg/kg b.i.d.	p.o.	3 days 4 weeks	Disturbance of balance, vomiting, prostration, dyspnea, loss of consciousness, death. Vomiting, incr. salivation, tremor, ataxia, one dog died at highest dose.
Dogs	Beagle	4	4	4	1M 1F	0, 5, 20, 40 mg/kg/day	p.o.	4 weeks	None
Dogs	Beagle	3	3	3	1M 1F	Saline, 0.5, 5 mg/kg/day	i.v.	2 weeks	Prolonged PR interval in ECG.
Dogs	Beagle	2	2	2	1M 1F	Saline, 5 mg/kg/day	i.v.	2 weeks	Prolonged PR interval in ECG.

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Chronic toxicity:

In chronic toxicity studies in rats and dogs administered metoprolol orally, test-compound related findings were limited to the dog with the observation of bradycardia, increase PR intervals and QT prolongation in a 6-month repeated dose toxicity study at the dosages of 0, 5, 20 and 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 months 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, and 60 mg/kg/day. In this study in the dog the high dosage of 120 mg/kg was given on Day 1, followed by 60 mg/kg/day 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.

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Chronic Toxicity in Animals

Species	Strain	Sex		No. of Groups	No. of Animals/Group	Dose mg/kg/day	Route	Duration of Study	Toxic Effects
		M	F						
Rats	Sprague-Dawley	60	60	4	15M 15F	Saline, 10, 100, 200 mg/kg/day. High dose increased to 200 mg/kg/day after 13 weeks.	p.o.	6M	None
Dogs	Beagle	11	11	Cont. 1 Active 3	2M 2F 3M 3F	0, 5, 20, 40 mg/kg b.i.d. After 7 W, high dose incr to 50 mg/kg b.i.d., after 3 M, intermediate dose increased to 30 mg b.i.d. and high dose to 80 mg b.i.d.	p.o.	6M	Bradycardia, incr. PR interval and QT interval in ECG.
Dogs	Beagle	24	24	Cont. 1 Active 3	6M 6F 6M 6F	0, 10, 60 mg/kg/day. High level dogs rec'd 120 mg/kg/day 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 balance.	p.o.	1Y	2 high dosed dogs died on Day 1, otherwise, none.

7 Genetic Toxicology

Summary based on previous findings for the RLD.

Genotoxicity studies (dominant lethal, mice; clastogenicity in somatic cells; salmonella/mammalian microsome mutagenicity assays; nucleus anomaly test in somatic interphase nuclei) were negative.

8 Carcinogenicity

Summary based on previous findings for the RLD:

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.

9 Reproductive and Developmental Toxicology

1) Summary based on previous findings for the RLD:

Teratogenicity in Rodents:

- Metoprolol increases post-implantation loss and decreases neonatal survival in rats at dosages up to 22 times the maximum daily human dose of 200 mg, when based on surface area. Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. These limited animal studies do not indicate direct or indirect harmful effects with respect to teratogenicity. [1]
- Dosages of 10, 50 and 200 mg/kg were administered orally to Sprague-Dawley rats son Days 6-15 of gestation. Each dose group consisted of 20 pregnant rats. Clinical signs, food consumption and body weights of pregnant animals were recorded regularly. Upon sacrifice on day 21 of pregnancy the uterine contents were examined to determine litter size, fetal loss, and litter and mean pup weights. All the living fetuses were prepared for either skeletal or visceral examination in order to study the incidence of abnormalities. Treatment with metoprolol did not adversely affect any of the parameters studied. [2, 3]

Teratogenicity in rabbits:

Metoprolol doses of 5, 12.5 and 25 mg/kg were administered orally to rabbits of the New Zealand White strain on Days 6-18 of gestation. Each dose group consisted of about 20 pregnant rabbits. Parent animals were considered to be unaffected by treatment, as assessed by clinical signs, change of body weight and pregnancy rate. Litter parameters, as assessed by litter size, fetal loss, and litter and mean pup weights, were not significantly affected by treatment although litter size was slightly low and fetal loss slightly high at 25 mg/kg. The incidence of fetal abnormalities appeared to be unaffected by treatment. [2, 3, 4]

Fertility and pre- and post-natal development in rodents:

- Metoprolol showed reversible effects on spermatogenesis in male rats starting at oral dosage level of 3.5 mg/kg, but had no effect on rate of conception at higher dosages in animal fertility studies. [4]
- Metoprolol dosages of 50 and 500 mg/kg were 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 in each group were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days post-partum. Upon sacrifice on day 13 of gestation the uterus with contents was weighed and corpora lutea, implantation sites, resorptions and foetal abnormalities were recorded. In females allowed to litter normally the duration of gestation, type of labor, delivery and lactation were recorded. The number, sex and the incidence of gross abnormalities of viable and stillborn pups were recorded. Pups were weighed at birth and 4, 7, 14 and 21 days post-partum.

Results: Survival, growth of pups and fertility of male and female rats were unaffected by medication. Pre-implantation survival of conceptuses from treated dams showed a slight, dose-related reduction from that of controls at midterm, but the differences were not statistically significant and reductions in the mean number of implantation sites did not occur in full term pregnancies. The post-implantation survival of embryos was unaffected. The mean number of viable newborns was significantly reduced in the high dose group while the low dose group was similar to controls. The reduction was attributable in part to the somewhat higher frequency of stillbirths noted in the high dose animals. In addition, the intrauterine growth rate of conceptuses was reduced slightly from that of controls, though not to a statistically significant degree, in both treatment groups. Postnatal survival of pups in the drug-treated groups showed a dose-related reduction compared to controls. The differences were statistically significant for the high dose group only. The postnatal growth of surviving pups, however, was not impaired. [2, 3]

- No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on mg/m² basis, the daily dose of 200 mg in a 60-kg patient. [1]

- Metoprolol dosages of 10, 50 and 200 mg/kg were administered orally to Sprague-Dawley rats from day 15 of gestation through lactation to 21 days postpartum. Each dosage group consisted of 20 pregnant rats. Clinical signs, food consumption and body weights of pregnant animals were recorded regularly. The duration of gestation, type of labor and delivery and lactation were also recorded. The parameters studied were litter size, litter and mean pup weights at birth and 4 and 21 days postpartum, cumulative fetal loss at 4 and 21 days postpartum and gross malformations. Neither parent nor litter parameters were adversely affected by the treatment with metoprolol. [2, 3]

1. Prescribing Information on TOPROL-XL (Metoprolol succinate) tablet, by AstraZeneca LP Wilmington, DE 19850, May 2014, Reference ID: 3501404
2. Product Monograph of TEVA-METOPROLOL (Metoprolol tartrate) 25 mg, 50 mg and 100 mg Tablets, Teva Canada Limited, 30 Novopharm Court, Toronto. Feb, 2014.
3. Nils-Olof Bodin, Hans Flodh, Goran Magnusson, Torbjorn Malmfors and Jan-Anders Nyberg. Toxicological studies on metoprolol. *Acta Pharmacol. et. toxicol.* 1975. 36, suppl. V, 96-103.
4. Prescribing Information on LOPRESSOR (Metoprolol tartrate) tablet, by Novartis Pharmaceuticals Corporation, Suffern, New York: Dec, 2012.

2) Summary based on new safety findings for metoprolol in the past 5 years (2014-present extracted from the literature):

This summary is based on one single literature article that the sponsor found relevant to this section.

In an experiment with chicks, embryotoxicity was tested *in ovo* after intra-amniotic injection of various doses (0, 2, 20, 40 200 µg) of metoprolol for a period of 30 min on Embryonic Day (ED) 4 and 8. On ED 9, wet and dry weight of embryo and heart rate was measured as a marker of embryotoxicity. In addition, the surviving embryos were thoroughly screened for external and internal malformations (limb defects, orofacial anomalies, body wall closure defects, gut defects, and microdissection of the heart).

No significant increase in mortality was observed in ED4 embryos injected with different doses of metoprolol, and 39% mortality was achieved in ED8 embryos injected with 200 µl of metoprolol. Metoprolol lead to a 33% decrease in heart rate measured 30 min after administration in ED4 *ex ovo* embryos compared with a 6% reduction from the baseline of 150 ± 13 beats/min (mean \pm SD) in the normal saline group. The cardiac output in ED4 embryos decreased by 1% from baseline in the control group compared to 16% from baseline in the metoprolol group. In more mature ED8 embryos, the negative chronotropic effect of metoprolol was even more pronounced, with the heart rate decreasing by 71% from baseline compared with the controls where the heart rate decreased only by 36% from baseline. The heart rate decreased concomitantly by 61% in the metoprolol group.

Although the number of β -adrenergic receptors has a tendency to decrease during embryonic development, the negative chronotropic effect of metoprolol was increasingly more pronounced with embryonic maturity. This effect was associated with reduced cardiac output in chick embryos, probably leading to premature death.[5]

5. Kockova R et al. Heart rate changes mediate the embryotoxic effect of antiarrhythmic drugs in the chick embryo. 2013. Am J Physiol Heart Circ Physiol 304: H895–H902

11 Integrated Summary and Safety Evaluation

No new preclinical studies were provided by the sponsor of this NDA.

- The pharmacology, metabolism, pharmacokinetic and safety pharmacology of metoprolol is based on Sponsor's summary of literature articles published in 1975 that include *in vitro* and *in vivo* studies to evaluate the acute hemodynamic effects, antihypertensive effects and β -receptor blocking activity of metoprolol in different species, and from extracts of the review of RLD. NDA019962.

- Sponsor provided an updated preclinical information package focusing on pharmacology, and reproductive toxicity findings since the last labelling update of 2014 for the RLD. Overall, the extensive review of non-clinical literature forecasts no new safety issues. Furthermore, systemic effects of metoprolol have already been well characterized and long clinical experience also provides enough evidence to support the safety of metoprolol at judicious doses.

- The toxicity findings are described in the monographs of generic drugs and the labels of the RLD. Acute effects observed at dosages used to determine LD50 included sedation, hypersensitivity, irritation and spasms in rats and mice. In sub-chronic and chronic toxicity studies in rats and dogs, toxicity, including death was observed mostly in the dog at the highest dosages.
- Reproductive toxicity studies did not reveal any teratogenic potential and any significant effect on embryo fetal development and fertility according to monographs and literature articles dated 1975.
- Review of the literature did not reveal any teratogenic potential of metoprolol. However, adverse effects of metoprolol on pregnancy, fertility and reproductive performance cannot be completely ruled out, and are described in the labeling.
- There was no evidence of genotoxic potential of metoprolol in a battery of *in vivo* and *in vitro* tests and carcinogenesis studies did not reveal any tumorigenic potential based on monographs.

12 Appendix/Attachments

Complete summary of pre-clinical findings provide by sponsor and extracted from the literature and public knowledge:

Primary Pharmacology:

- Metoprolol is a β -adrenergic receptor-blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on the β 1-adrenoreceptors, chiefly located in cardiac muscle.
- This preferential effect is not absolute, however, and at higher doses, metoprolol also inhibits β 2- adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and unlike propranolol, membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction. Metoprolol has competitive ability to antagonize catecholamine-induced tachycardia at the β -receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output as well as inhibition of the vasomotor centers and renin release by the kidneys.

Beta-receptor blocking activity:

In vitro:

Studies in isolated rat atria indicate that metoprolol is a competitive inhibitor of the chronotropic and ionotropic responses to isoprenaline. *In vitro* studies of the interaction of metoprolol or propranolol and isoprenaline have also been carried out in the right atrium and the trachea of the guinea pig. Metoprolol was about ten times more potent at blocking the cardiac chronotropic response than the tracheal smooth muscle relaxant response to isoprenaline. Propranolol, on the other hand, showed about the same inhibitory potency in both tissues. These *in vitro* findings supports that metoprolol is a competitive β 1-selective antagonist [Ablad, 1975].

In vivo:

- Metoprolol had β 1-selective blocking properties also in *in vivo* studies. The following table (Table 1), summarizes the comparative potencies (in terms of ED₅₀) of metoprolol, propranolol

and practolol using the reserpinized anaesthetized cat model to study the effect on heart rate and vascular resistance and the guinea pig model exposed to histamine mist to study the effect on bronchial pathway.

Table 1: Comparative Potencies (ED₅₀) of Metoprolol, Propranolol and Practolol

Substance	ED ₅₀ (mg/kg i.v.) for blockade of response			
	Sympathetic nerve stimulation	Isoprenaline		
	Heart rate	Heart rate	Peripheral vascular resistance	Bronchial smooth muscle
Metoprolol	0.1	0.4	5	3
Propranolol	0.1	0.1	0.1	0.1
Practolol	0.1	0.5	35	4

- In the reserpinized anaesthetized cat 1, metoprolol was about three times a less potent inhibitor of the cardiac chronotropic response to isoprenaline than propranolol and 50 times less potent with regard to inhibition of the peripheral vasodilator response to isoprenaline. Further metoprolol was also found to be much less active than propranolol with regard to the inhibition of the bronchodilator effect of isoprenaline in the guinea pig studies. Practolol showed a somewhat higher degree of β_1 -selectivity in these tests than metoprolol while propranolol was non-selective.

- Metoprolol (like practolol) was found to inhibit the cardiac chronotropic response to sympathetic nerve stimulation more markedly than the response to isoprenaline, whereas no potency difference was found for propranolol. Metoprolol was equipotent to propranolol with regard to blockade of the cardiac response to sympathetic nerve stimulation. Metoprolol was found to be approximately equipotent to propranolol with regard to inhibition of the noradrenaline-induced increase of plasma free fatty acids in anaesthetized dogs. This effect probably reflected β_1 -receptor blockade of the lipolytic effect of noradrenaline in adipose tissue [Ablad, 1975].

- It has been shown that adrenergically induced release of renin from the kidneys is mediated by a β -receptor. Metoprolol and propranolol were found to be approximately equipotent inhibitors of the renin release response to low frequency stimulation of the renal sympathetic nerves in the anaesthetized dog. This result indicated that β_1 -receptors are involved in the release of renin caused by noradrenaline liberated from adrenergic neurons [Ablad, 1975].

- Studies in reserpinized cats showed that metoprolol was devoid of β -receptor stimulating (intrinsic) activity [Ablad, 1975].

- Metoprolol and propranolol showed marked differences in their interaction with adrenaline, since to a great extent it involves β_2 -receptors. One prominent β -receptors mediated cardiovascular effect of lower doses of adrenaline is dilatation of resistance vessels in skeletal muscle. In the hind leg of the anaesthetized cat, metoprolol even up to 2 mg/kg dose by intravenous route did not affect the vasodilator response to adrenaline, indicating insignificant vascular β -blockade. Propranolol, on the other hand, reversed the vasodilator effect of

adrenaline at only 0.1 mg/kg. In accordance with these findings, propranolol was found to potentiate the pressor response to adrenaline in the anaesthetized cat, whereas metoprolol, in i.v. doses of 0.1-2 mg/kg did not alter the effect of adrenaline on blood pressure [Ablad, 1975]. Based on these results, it can be concluded that metoprolol resembles propranolol in being devoid of intrinsic activity on β -receptors (agonist effect). At an i.v. dose of 0.5 mg/kg, both compounds produced marked and approximately equal inhibition of the cardiac, lipolytic and renin release responses to noradrenaline, i.e. responses that are mainly mediated by β_1 receptors. At this dosage metoprolol and propranolol exerted, however, markedly different effects on β_2 -mediated effects, i.e. metoprolol does not significantly inhibit the bronchodilator and vasodilator responses to isoprenaline or adrenaline, while propranolol produces marked blockade [Ablad, 1975].

- Selectivity studies with metoprolol have revealed no important pharmacodynamic effects other than those attributable to β -blockade. The cardio stimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg metoprolol in the anaesthetized cat. The same dosage of metoprolol was found to be devoid of anticholinergic, ganglionic blocking, antihistaminic and alpha-receptor blocking properties in cats.

- In doses far above those eliciting marked cardiac β -blockade, metoprolol, like other β -blockers, produced a cardio depressant effect in reserpinized cats. It has been reported that this action of β -blockers is directly correlated to their fat:water partition coefficient. This coefficient is considerably lower for metoprolol than for propranolol, accounting for the greater local anesthetic effect of the latter. In agreement with this, metoprolol had a distinctly weaker cardiodepressant action than propranolol in reserpinized cats, a significant negative chronotropic and inotropic effect observed only after doses of metoprolol greater than 10 mg/kg i.v. The results of these studies indicate that metoprolol is a specific β -blocker [Ablad, 1975].

Acute hemodynamic effects:

- Metoprolol at 0.1-0.5 mg/kg dose i.v. markedly inhibited cardiac chronotropic and inotropic responses to sympathetic nerve stimulation in the cat, and the compound was equipotent to propranolol in this respect.

- The general hemodynamic effects of metoprolol and propranolol, at i.v. doses of 0.1 and 0.5 mg/kg, were studied in the dog. When given to anaesthetized dogs with acute cardiac denervation, the blockers produced practically no hemodynamic effects. In studies on conscious dogs pre-treated with methscopolamine, the blockers produced equal and dose-dependent reductions of the heart rate, left ventricular contractility and cardiac output, the effects being moderate in resting dogs and more marked in dogs exercising on a treadmill. In these studies on conscious dogs the blockers elicited no or only a slight reduction of the mean arterial blood pressure. The diminished cardiac output was accompanied by an increase of the total peripheral vascular resistance (baroreceptor reflex mechanisms) [Ablad, 1975].

- Metoprolol is a much weaker inhibitor of the peripheral vasodilator effect of adrenaline than propranolol. It was considered to be of interest to compare how the two blockers influenced the general hemodynamic effects of adrenaline in conscious dogs pretreated with methscopolamine. Adrenaline was infused i.v. in a dose that produced modest hemodynamic effects, consisting of reduced total peripheral vascular resistance and increased cardiac output with a tendency to diminished arterial blood pressure. Propranolol changed this effect pattern dramatically. After propranolol (0.1 and 0.5 mg/kg i.v.) adrenaline increased the arterial blood pressure by about 60mm Hg. The increased cardiac afterload resulted in a marked reduction of the stroke volume

with a pronounced increase of the end diastolic diameter of the left ventricle. After metoprolol (0.1 and 0.5 mg/kg i.v.), on the other hand, adrenaline caused no significant increase of the arterial blood pressure, and its hemodynamic effects were generally not much affected [Ablad, 1975].

- The above described hemodynamic interaction patterns could not be reproduced in studies on conscious dogs, which were not given anticholinergic pretreatment. In these experiments, the hypertensive effect of adrenaline in propranolol-treated dogs was accompanied by a marked bradycardia, indicating a reflex increase of vagal tone on the heart [Ablad, 1975].

These results suggested that in situations in which there is a significant release of adrenaline from the adrenal medulla into the circulation, the total peripheral vascular resistance and the arterial blood pressure should be lower during metoprolol treatment than during treatment with propranolol [Ablad, 1975].

Antihypertensive effects:

- The mechanism of the antihypertensive effects of beta-blocking agents has not been fully elucidated. One single dose of metoprolol or propranolol reduces the blood pressure only slightly, as the reduced cardiac output is associated with raised total peripheral vascular resistance. After a few days of continued treatment there is, however, a decrease of the arterial blood pressure which appears to be associated with a gradual return of the total peripheral vascular resistance towards the pretreatment level [Ablad, 1975].

- It has been found difficult to reproduce the clinically observed antihypertensive effect of β -blockers in hypertensive animals. However, the long-term treatment with metoprolol or propranolol inhibited the development of high blood pressure in young rats of a genetically hypertensive strain. This antihypertensive effect was found to persist for weeks after cessation of β -blocker administration [Ablad, 1975].

- In a study, 0.1% metoprolol and propranolol were administered in drinking water to hypertensive rats of age 1 to 7 months. Two days after the cessation of β -blocker administration, the rats were sacrificed and the contractile response to exogenous or neuronally released noradrenaline in a portal vein preparation was studied. It was observed that β -blocker treatment had not changed the noradrenaline dose-response curve in the portal vein preparation. The frequency response curve to electrical field stimulation was, however, characterized by a moderate but statistically significant depression within the low, "physiological" frequency range (0.5-2 Hz) in the preparations taken from animals treated with a β -blocker compared to those taken from untreated controls. These results indicated that the preventive antihypertensive effect of β -blockers in rats was associated with a reduction of the amount of noradrenaline released per nerve impulse from peripheral adrenergic nerves. This action may contribute to the reduction of the peripheral vascular resistance seen during repeated administration of β -blockers. The primary site of attack in this mechanism may be located in the peripheral adrenergic neuron. Such an action has been demonstrated in acute studies with propranolol and metoprolol in a muscle preparation of the hind leg of the cat. These blockers produced a moderate reduction in the vasoconstrictor response to the electrical stimulation of the sympathetic nerves. This effect was associated with a reduced release of noradrenaline into the venous outflow of the preparation. The findings may reflect the existence of an adrenergic presynaptic β_1 -receptor mediating a positive feedback on nor-adrenaline release [Ablad, 1975].

Secondary Pharmacology:

- Metoprolol is a selective β -adrenergic receptor-blocking agent and studies have revealed no important pharmacodynamic effects other than those attributable to β -blockade. In one acute study in anesthetized dogs, β_1 -receptors were inhibited at low doses but β_2 receptors were inhibited at higher doses of metoprolol with non-specific lethal cardiac depression [NDA 019962].
- It has also been shown that β -blockers may have a target in the central nervous system, leading to reduced sympathetic outflow to the periphery. It is possible that a long-term decrease of central sympathetic outflow will cause some reduction of the efficiency of the peripheral neuronal release of nor-adrenaline [Ablad, 1975].
- Metoprolol inhibited the increase in plasma renin activity induced by furosemide [NDA 019962]. The clinically observed antihypertensive effect of β -blockers is associated with reduced plasma renin activity. Diminished activity of the renin-angiotensin system may lead to reduced neuronal release of noradrenaline, because angiotensin has been shown to facilitate sympathetic nerve activity through actions both in the central nervous system and in the peripheral adrenergic nerves [Ablad, 1975].
- Metoprolol showed a negligible local anaesthetic effect on the isolated sciatic nerve of the frog and in the intracutaneous wheal test in guinea pigs. Propranolol has marked local anesthetic activity, i.e., up to approximately 50% of that of xylocaine.
- The effects of metoprolol in isoproterenol-stimulated metabolic effects showed inhibition of the increase in liberation of glycerol, glucose, insulin and free fatty acids [NDA 019962, CDER, 1991].

Safety pharmacology:

Long clinical experience of metoprolol reveals that there is no particular safety concern for metoprolol at judicious doses. There is a paucity of reported studies related to the safety pharmacology of metoprolol. In one cardiovascular safety study, dose related myocardial depressant activity of metoprolol succinate was reported. The metoprolol dosage causing cardiac depression (i.e approx.. 40% reduction in blood pressure and LVdp/dt) in anesthetized dogs was 15 micromoles/kg of either the succinate or the tartrate salt vs. 0.22 micromoles/kg required for beta-blockade (i.e., approx.. 40% inhibition of the beta adrenoceptor mediated tachycardiac effect of cardio-accelator nerve stimulation). Accordingly, the safety ratio for direct cardiac depressant activity vs. beta-blocking activity in dog (15/0.22) is approximately 70. These results evidence direct cardiac depressant activity, attributed to membrane stabilizing activity, is detectable only at plasma concentrations much greater than required for beta-blockade [NDA 019962-S013, CDER, 2001].

Toxicokinetics:**ADME:**

Metoprolol is rapidly and completely absorbed from the gastrointestinal tract in various species. The maximum concentration in plasma after oral administration of the drug in an aqueous solution is reached within 2 hours in the dog (10 and 20 mg/kg orally, single dose) and the rat (100 mg/kg orally, single dose) (Table 2). Metoprolol is extensively distributed to extra vascular tissues in all the species. After oral administration to a certain extent, metoprolol is metabolized in the liver through first pass. Metoprolol penetrates into the brain in mice and rat study. The ratio between brain and plasma concentration was about 5:1 in the rat. In the pregnant mouse, moderate concentrations of the drug could be recovered in the fetus. Metoprolol is eliminated

from the body by biotransformation and excretion in the urine mainly as metabolites in all species studied. The elimination half-life from plasma increases in the species studied in the order rat, cat, and dog. The rate of elimination seems to be independent of dose and route of administration [Borg, 1975].

Table 2. Pharmacokinetic properties of Metoprolol.

Species	T _{max} (hr)	Vd (l/kg)	t _{1/2} (hr)	Cp (20%) [±] (µg/ml)
Rat	0.5	6.3	0.6	-
Cat**	-	5.5	1.3	-
Dog	0.5-1.5	3.1	1.6	0.03

* Cp (20%) : Plasma Concentration at 20% reduction of exercise tachycardia

** Anaesthetized

To evaluate the urinary excretion of the test compound, metoprolol- (3H), was administered to dogs and rats at 20 mg/kg and 100 mg/kg single doses respectively by oral route. In dogs the radioactivity was almost completely excreted in the urine within 24 hours while in the rat, part of the dose was excreted in the faeces [Borg, 1975].

Table 3. Urinary excretion of total radioactivity in percent of given dose of Metoprolol- (³H) in dogs and rats

Species	Dose	Sampling interval	Amount excreted in % of dose
Dog	No 1 10 mg/kg p.o.	0-6 h	65
		6-24 h	24
	No 2 20 mg/kg p.o.	0-24 h	72
Rat	No 1 + 2 100 mg/kg p.o.	0-24 h	73

The main urinary metabolites in man, dog and rat were formed by oxidative deamination, o-dealkylation with subsequent oxidation and by aliphatic hydroxylation. In man, 65 % of the total amount of the main metabolite (metabolite I) was accounted in the urine. One of the metabolites, hydroxylated metoprolol, and an intermediate to the main metabolite were β-blockers with the same pharmacological profile as the parent drug but with lower potency. The three main urinary metabolites in man were recovered in urine from the dog and the rat, though the relative abundances of these metabolites in these two animal species were somewhat different to that in man (Table 4). Metabolite II was found in considerably lower relative amounts in the rat than in dogs and aliphatic hydroxylation of the methoxyethyl group seems to be a more pronounced route of metabolism in the rat. In the dog, metabolite II was found in higher amounts and metabolite I in lower amounts than in man. In these studies there was no indication of any additional main metabolites in dog and rat compared to man but a number of minor metabolites were detected in these species [Ablad, 1975, Borg, 1975].

Table 4. Relative abundances of the main urinary metabolites of Metoprolol in the dog and rat.

Species	Dose	Relative abundance % of amount excreted		
		Metabolite I	Metabolite II	Metabolite III
Dog	10 mg/kg p.o.	33	21	9
Rat	100 mg/kg p.o.	62	1	25
Man	50 mg/kg p.o.	65	10	10

Kinetics of the pharmacological effect of metoprolol:

Metoprolol induces cardiac β -blockade after intravenous administration in dogs. The effect of Metoprolol on tachycardia is linearly related to the logarithm of the plasma concentration of the parent drug in dogs. The concentration levels for significant β -blockade in the conscious dog and in man are within the same range. The effect on the exercise heart rate declines at a constant rate in the conscious dog and in man after intravenous and oral dose. The duration of action of the drug increases with the magnitude of the dose due to the linear decline of the effect with time. The effect on exercise tachycardia is reduced to 50 % of its maximum in about 4 hours in conscious dogs at a single dose of 1 mg/kg intravenously with an elimination half-life of about 1.5 hours [Ablad, 1975].

Pharmacological and toxicological properties of the metabolites:

The β -receptor blocking activity of metoprolol and its urinary metabolites were tested in reserpinized (5 mg/kg i.m. 24 hours before the experiment), anaesthetized and vagotomized cats. The ED₅₀ values for blockade of heart rate, cardiac contractile force and vasodilatation responses to isoprenaline are reported in Table 5.

Table 5. Pharmacological (ED₅₀) and Toxicological (LD₅₀) Effects of Metoprolol and its Metabolites

Substance	β - receptor blocking activity ED ₅₀ (mg/kg i.v.)			Toxicity LD ₅₀ (mg/kg i.v.)
	Heart rate	Contractile force	Vasodilation	
Metoprolol	0.3 ± 0.09	0.3 ± 0.06	3.9 ± 0.70	60
Metabolite III	3.0 ± 0.90	1.5 ± 0.50	27 ± 9.2	200
H 105/22	2.7±0.77	2.5 ± 0.84	8.9 ± 3.1	150
Metabolite II	>34	>34	>32	>500
Metabolite I	>34	>34	>32	>500

At the administered doses (up to 34 mg/kg), the metabolites I and II did not influence the responses to isoprenaline. Metabolite III and the substance H 105/22, a presumed metabolite, blocked the studied responses to isoprenaline but these two compounds were less potent than metoprolol both regarding blockade of the cardiac and the vascular responses.

None of the compounds showed an intrinsic beta-mimetic activity. The acute toxicity of metoprolol and its urinary metabolites were tested in the mouse by intravenous route. The LD50-values demonstrate a lower acute toxicity in the mouse for all four tested compounds than for metoprolol (Table 5 above) [Borg, 1975].

Toxicity:

Single dose toxicity in rodents:

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 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; Bodin, 1975].

Table 6: Calculated LD₅₀ values

Species	Sex	Route	Solutions	LD ₅₀ (mg/kg body weight)
Mouse	male	i.v.	1%	69.40 ± 5.08
Mouse	female	i.v.	1%	79.90 ± 4.47
Mouse	male	p.o.	23%	2460 ± 210
Mouse	female	p.o.	25%	2300 ± 200
Rat	male	i.v.	5%	71.94 ± 4.14
Rat	female	i.v.	5%	74.30 ± 4.44
Rat	male	p.o.	50%	4670 ± 1210
Rat	female	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].

Repeat-dose toxicity:

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 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 Teva- Metoprolol (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 dosages 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 block 4 hours after the first dose and 1 hour after the second dose on Day 41 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 7 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].

Genotoxicity:

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].

Rodent Carcinogenicity:

Metoprolol was administered in the diet to provide 50, 200 and 800 mg/kg per day for 78 weeks to Charles River Sprague-Dawley rats. The incidences of nodules and masses observed at necropsy were similar between the treated and control groups. Pathologic changes were observed that consisted of an increased incidence of “impaction of pulmonary alveoli by septal cells in the high and intermediate metoprolol treated groups”.

A carcinogenicity study in Swiss albino mice at the dosages of 75, 150 and 750 mg/kg per day for 78 weeks did not show evidence of drug-induced excess neoplastic tumors [Prescribing Information on Lopressor (Metoprolol tartrate) tablets, Novartis, 2012; Product Monograph of Teva- Metoprolol (Metoprolol tartrate) tablets, Teva, 2014].

Reproductive and 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].

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].

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