PRODUCT MONOGRAPH

Pr Metoprolol Tartrate Injection USP

5 mg / 5 mL (1 mg / mL) Solution

ß-Adrenergic Receptor Blocking Agent

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[Pr] Metoprolol Tartrate Injection USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous Injection	Solution / 5 mg/5 mL (1 mg/mL)	Sodium chloride and water for injection

INDICATIONS AND CLINICAL USE

Myocardial Infarction

Metoprolol Tartrate Injection USP is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction, to reduce cardiovascular mortality.

Treatment with Metoprolol Tartrate Injection USP can be initiated as soon as the patient's clinical condition allows (***see Dosage and Administration, Contraindications, and Warnings and Precautions***).

Clinical trials have shown that patients with unconfirmed myocardial infarction received no benefit from early metoprolol tartrate therapy.

Geriatrics:

Caution is indicated when using Metoprolol Tartrate Injection USP in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Pediatrics:

No pediatric studies have been performed. The safety and efficacy of metoprolol tartrate in pediatric patients have not been established.

CONTRAINDICATIONS

Metoprolol Tartrate Injection USP (metoprolol tartrate) should not be used in the presence of:

- Known hypersensitivity to metoprolol and derivatives, Metoprolol Tartrate Injection USP components, or hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur)
- Sinus bradycardia
- Sick sinus syndrome
- Second and third degree A-V block
- Right ventricular failure secondary to pulmonary hypertension
- Overt heart failure
- Cardiogenic shock
- Severe peripheral arterial circulatory disorders
- Anesthesia with agents that produce myocardial depression, (e.g., ether)
- Untreated pheochromocytoma
- Asthma and other obstructive respiratory diseases

Myocardial Infarction Patients - Additional Contraindications

Metoprolol tartrate is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (PR interval ≥ 0.24 s); systolic blood pressure < 100 mmHg; or moderate to severe cardiac failure (see ***Warnings and Precautions***).

WARNINGS AND PRECAUTIONS

General

Cardiovascular system: Special caution should be exercised when administering metoprolol tartrate to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. The positive inotropic action of digitalis may be reduced by the negative inotropic effect of metoprolol

tartrate when the two drugs are used concomitantly. The effects of β-blockers and digitalis are additive in depressing A-V conduction. This also applies to combinations with calcium-antagonists of the verapamil type or some antiarrhythmics (see ***Drug Interactions***).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure and/or hypotension (systolic blood pressure ≤ 90 mmHg). Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol tartrate therapy should be reduced or withdrawn.

Cardiovascular

Severe Sinus Bradycardia: Severe sinus bradycardia may occur after β_1-adrenergic receptor blockade with metoprolol tartrate because of unopposed vagal activity. Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated, possibly leading to A-V block. In such cases, dosage should be reduced or gradually withdrawn. Atropine, isoproterenol or dobutamine should be considered in patients with acute myocardial infarction.

Prinzmetal's angina: Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris).

Peripheral Circulatory Disorders: Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Myocardial Infarction - Additional Warnings

Acute Intervention: During acute intervention in myocardial infarction, intravenous metoprolol tartrate should only be used by experienced staff under circumstances where resuscitation and monitoring equipment is available.

Cardiac Failure: Depression of the myocardium with metoprolol tartrate may lead to cardiac failure (see general ***Warnings*** above). Special caution should be exercised when administering metoprolol

tartrate to patients with a history of cardiac failure or those with minimal cardiac reserve. Should failure occur, treatment should be as described in **WARNINGS**.

Severe Sinus Bradycardia*:** Severe sinus bradycardia may occur with metoprolol tartrate use (see general ***Warnings above). Acute myocardial infarction (particularly inferior infarcts) may significantly decrease sinus rate. If the rate falls below 40 beats/min, especially with signs of decreased cardiac output, administer atropine (0.25-0.5 mg) intravenously. If atropine treatment is unsuccessful, discontinue metoprolol tartrate and consider cautious administration of isoproterenol or installation of a cardiac pacemaker.

A-V Conduction: Metoprolol tartrate slows A-V conduction and may produce significant first- (PR interval ≥ 0.24 sec), second-, or third-degree heart block. Acute myocardial infarction may also produce heart block. If heart block occurs, discontinue metoprolol tartrate and administer atropine (0.25-0.5 mg) intravenously. If atropine treatment is unsuccessful, consider cautious administration of isoproterenol or installation of a cardiac pacemaker. Because of their negative effect on atrioventricular conduction, beta-blockers, including metoprolol tartrate, should only be given with caution to patients with first degree atrioventricular block.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, metoprolol tartrate should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or A-V block, treatment should be directed at reversing these (see above).

Abrupt withdrawal

Patients with angina or hypertension should be warned against abrupt discontinuation of metoprolol tartrate. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of β-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina

pectoris. Therefore, when discontinuation of metoprolol tartrate is planned in patients with angina pectoris or previous myocardial infarction, the dosage should be gradually reduced over a period of about two weeks. The patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, metoprolol tartrate therapy should be discontinued stepwise and with closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with metoprolol tartrate be reinstituted promptly, at least temporarily.

Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it is prudent not to discontinue metoprolol tartrate therapy abruptly even in patients treated only for hypertension.

Endocrine and Metabolism

Thyrotoxicosis: Although metoprolol has been used successfully for the symptomatic (adjuvant) therapy of thyrotoxicosis, possible deleterious effects from long-term use of metoprolol tartrate have not been adequately appraised. ß-blockade may mask the clinical signs of continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of metoprolol tartrate may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Diabetic patients: Metoprolol tartrate should be administered cautiously to patients spontaneously hypoglycemic or diabetic patients who are receiving insulin or oral hypoglycemic agents. ß-adrenergic receptor blockers, including metoprolol tartrate , affect glucose metabolism and may mask the premonitory signs and symptoms of acute hypoglycemia, such as tachycardia. In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, beta-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need adjustment. Diabetic patients receiving metoprolol tartrate should be monitored to ensure that diabetes control is maintained.

Pheochromocytoma: Where a ß-blocker is prescribed for a patient known to be suffering from a

pheochromocytoma, an alpha-blocker should be given concomitantly and only after the alpha-blocker has been initiated.

Hepatic/Biliary/Pancreatic

Metoprolol tartrate is mainly eliminated by means of hepatic metabolism (see ***Actions and Clinical Pharmacology - Pharmacokinetics***).

Hepatic impairment: may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Therefore, metoprolol tartrate should be used with caution in patients with impaired liver function. Liver function tests should be performed at regular intervals during long-term treatment (*see* ***Actions and Clinical Pharmacology, Pharmacokinetics***). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Therefore, dose adjustment and regular monitoring of hepatic function are advised in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should be treated with caution i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs.

Interactions

Calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol tartrate because there is a risk of cardiac arrest in this situation (see ***Drug Interactions***). Patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol tartrate should be closely monitored. See the complete list of observed and potential drug-drug and other drug interactions with metoprolol tartrate in the ***Drug Interactions*** section.

Peripheral vascular disease:

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see ***Contraindications***).

Peri-Operative Considerations

***Anesthesia and Surgery*:** The necessity or desirability of withdrawing beta-blocking agents prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anaesthesia and surgical procedures. The benefits of continuing a treatment with a beta-blocker should be balanced against the risk of withdrawing it in each patient. However, care should be taken to avoid using anesthetic agents that may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg i.v.).

In patients receiving beta-blocker therapy, inhalation anaesthetics may enhance the cardiodepressant effect. Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported.
Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Since metoprolol is a competitive inhibitor of ß-adrenoceptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or dobutamine.

Renal

Renal impairment: In patients with severe renal disease, haemodynamic changes following beta-blockade may impair renal function further. Beta-blockers which are excreted mainly by the kidney may require dose adjustment and safety monitoring in patients with severe renal impairment, including renal failure.

Respiratory

Bronchospastic Diseases: **In general, patients with bronchospastic diseases should not receive ß-blockers, including** metoprolol tartrate. However, because of its relative $ß_1$-selectivity, metoprolol tartrate may be used with caution in patients with asymptomatic bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $ß_1$-selectivity is not absolute, a $ß_2$-stimulating agent should preferably be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer metoprolol tartrate in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see ***Dosage and Administration***).

Because it is unknown to what extent $ß_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically in patients with proven or suspected acute myocardial infarction. If bronchospasm not related to congestive heart failure occurs, metoprolol tartrate should be discontinued. A theophylline derivative or a $ß_2$-agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $ß_2$-agonists may produce serious cardiac arrhythmias.

Sensitivity/Resistance

***Anaphylactic reactions*:** There may be increased difficulty in treating an allergic type reaction in patients on ß-blockers. Whenever possible, ß-blockers, including metoprolol tartrate, should be avoided in patients who are at risk of anaphylaxis. In these patients, the reaction may be more severe due to pharmacologic effects of the ß-blockers and problems with fluid changes. Epinephrine should be

administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of ß-agonists including parenteral salbutamol or isoproterenol, to overcome bronchospasm and norepinephrine to overcome hypotension.

Skin

Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported with ß-blockers, including metoprolol tartrate. Oculomucocutaneous syndrome, a severe syndrome whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one ß-adrenergic receptor-blocking agent (practolol). This syndrome has not been observed with metoprolol tartrate or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur. (see ***Warnings and Precautions – Abrupt withdrawal)***.

Special Populations

Women of child-bearing potential: Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor and stop gradually taking the drug. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against the possible hazards.
Pregnant Women: There is a limited amount of data on the use of metoprolol in pregnant women. Metoprolol crosses the placental barrier. Since metoprolol tartrate has not been studied in human pregnancy, the drug should not be given to pregnant women.

Nursing Women: Metoprolol is excreted in breast milk. If drug use is essential, patients should stop nursing.

Pediatrics: No pediatric studies have been performed. The safety and efficacy of metoprolol tartrate in pediatric patients have not been established.

Geriatrics: Caution is indicated when using metoprolol tartrate in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels. Lower starting and maintenance doses and safety monitoring are advised in these patients (see ***Indications and Clinical use, Dosage and Administration, and Actions and Clinical Pharmacology - Pharmacokinetics - Special populations***).

Driving and using machines

Dizziness, fatigue or visual impairment may occur during treatment with metoprolol tartrate (see ***Adverse Drug reactions***) and may adversely affect the patient's ability to drive or use machines.

Patients should be advised to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to metoprolol tartrate therapy has been determined.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events reported are exertional tiredness, gastrointestinal disorders, and disturbances of sleep patterns. The most serious adverse events reported are congestive heart failure, bronchospasm and hypotension.

Reported adverse events according to organ systems are:

Cardiac disorders	Secondary effects of decreased cardiac output which include: syncope, vertigo, light-headedness and postural hypotension; Significant Conduction disorders (First, Second and third degree A-V block) (***see Contraindications***); Congestive heart failure (***see Warnings***);

	Severe bradycardia; Hot flushes; Arrhythmias; Lengthening of PR interval; Palpitations; Sinus arrest; Cold extremities; Claudication; Chest pain
Vascular disorders	Raynaud's phenomenon; Gangrene in patients with pre-existing severe peripheral circulatory disorders; Oedema
Psychiatric disorders	Mental depression; Vivid dreams / nightmares; Hallucination; Personality disorder
Nervous System disorders	Headache, Weakness, Dizziness, Sedation, Light-headedness, Somnolence, insomnia, Vertigo, Paresthesia, Anxiety, Depressed level of consciousness
Gastrointestinal disorders	Diarrhea, Abdominal pain, Constipation, Heartburn, Flatulence, Dry mouth, Nausea and vomiting, Retroperitoneal fibrosis
Hepatobiliary disorders	Hepatitis
Respiratory disorders	Shortness of breath; Wheezing; Bronchospasm; Rhinitis; Status asthmaticus; Exertional dyspnea
Skins and subcutaneous tissue disorder (*see Warnings)*	Rash (exanthema, urticaria, psoriasiform and dystrophic skin lesions; Hyperhydrosis; Pruritus; Photosensitivity reaction; Alopecia; Worsening of psoriasis
Musculoskeletal and connective tissue disorders	Muscle spasms; Arthritis
Reproductive system and breast disorders	Erectile dysfunction; Libido disorder; Peyronie's disease
Ear and labyrinth disorders	Tinnitus; Hearing disorders (e.g. hypoacusis or deafness) when doses exceed those recommended
Eye disorders	Dry eyes, eye irritation; Visual impairment (e.g. blurred vision); Conjunctivitis

General disorders and administration site conditions	Fatigue; Exertional tiredness
Metabolism	Weight increase

Adverse reactions in clinical trials

In a placebo-controlled study in patients with acute myocardial infarction the incidence of the following cardiovascular reactions were:

	Metoprolol	Placebo
Orthostatic hypotension (systolic BP < 90 mmHg	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (PR ≥ 0.24 s)	5.3%	1.9%
Cardiac failure	27.5%	29.6%

Abnormal Hematologic and Clinical Chemistry Findings

Clinical Laboratory

The following laboratory parameters have been elevated on rare occasions: transaminases, BUN, alkaline phosphatase and bilirubin.

Hematology

Isolated cases of thrombocytopenia and leucopenia.

Post-Market Adverse Drug Reactions

The following adverse reactions have been derived from post-marketing experience with metoprolol tartrate or via spontaneous case reports and literature cases. Because these reactions are reported voluntary from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions

are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Nervous system disorders

Confusional state

Investigations

Blood triglycerides increased, High Density Lipoprotein (HDL) decreased

DRUG INTERACTIONS

Overview

Established or Potential Drug-Drug Interactions

(Legend: CT = Clinical Trial; C=Postmarket (Case Study); T = Theoretical)

Metoprolol	Ref	Effect	Clinical comment
Alcohol	C	Increased concentration of metoprolol in blood	Metoprolol modifies the pharmacokinetics (decreases the elimination rate) of alcohol. Which *may* increase certain side effects of metoprolol
Anti-adrenergic agents	C	Potentiate antihypertensive effect of alpha-adrenergic blockers	Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by ß-blockers. ß-adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia. On the contrary, ß-adrenergic blockers may also potentiate the hypertensive response to withdrawal of clonidine as patients receiving concomitant clonidine and ß-adrenergic blocker. Withdrawing the ß-blocker several days before the clonidine may reduce the danger of rebound effects.

Metoprolol	Ref	Effect	Clinical comment
Antiarrhythmic Agents	C	Potentiate the negative inotropic effect of antiarrhythmic agents and their effect on atrial conduction time	ß-blockers may potentiate the negative inotropic effect of anti-arrhythmic agents and their effect on atrial-conduction time. Particularly, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest, and atrioventricular block antiarrhythmic agents such as quinidine, tocainide, procainamide, ajmaline amiodarone, flecainide and disopyramide may potentiate the effects of metoprolol tartrate on heart rate and atrioventricular conduction.
Other Antihypertensive drugs	CT	Hypertension	metoprolol tartrate dosage should be adjusted to the individual requirements of the patient especially when used concomitantly with other antihypertensive agents (see ***Dosage and Administration***). Patients receiving concurrent treatment with catecholamine depleting drugs, other beta-blockers (including those in form of eye drops, such as timolol), or monoamine oxidase (MAO) inhibitors, should be carefully monitored. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.
Calcium Channel Blockers (IV use)	CT	Potentiate the depressant effects of ß-blockers	Calcium channel blockers such as verapamil and diltiazem may potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and atrioventricular conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol tartrate because there is a risk of cardiac arrest in this situation. However, in exceptional cases, when the physician considers

Metoprolol	Ref	Effect	Clinical comment
			concomitant use essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists. Verapamil and diltiazem reduce metoprolol clearance. (see ***Warnings and Precautions***)
Calcium channel blockers (oral use)	CT	Additive reduction in myocardial contractility	Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol tartrate should be closely monitored.
CYP2D6 inhibitors	CT	↑ plasma concentration of metoprolol	Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer (see Clinical Pharmacology). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinine, antifungals such as terbinafine.
Digitalis glycosides	C	Excessive bradycardia and/or ↑ in	Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular

Metoprolol	Ref	Effect	Clinical comment
		atrioventricular conduction time	conduction time. Monitoring heart rate and PR interval is recommended.
Dipyridamole	C	Careful monitoring of heart rate	In general, administration of a ß-blocker should be withheld before dipyridamole testing, with careful monitoring of heart rate following the dipyridamole injection.
Ergot alkaloid	C	↑ vasoconstrictive action of ergot alkaloids	Concomitant administration with ß-blockers may enhance the vasoconstrictive action of ergot alkaloids.
Fingolimod	CT/C	Bradycardia	Concomitant administration of beta-blockers with other drugs known to decrease heart rate such as sphingosine-1-phosphate receptor modulators (e.g. fingolimod) may result in additive heart rate lowering effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.
Hepatic Enzyme-Inducers	CT	Influence plasma level of metoprolol	Hepatic enzyme-inducing substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by rifampicin.
Hydralazine	C	↑ concentrations of metoprolol	Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.
Inhalation anesthetics	C	↑ cardiodepression of certain anesthetics	ß-blockers enhance the cardiodepression produced by certain anesthetics (see ***Warnings and Precautions - Patients Undergoing Surgery***).
Lidocaine	C	↓ clearance of lidocaine	Metoprolol may reduce the clearance of lidocaine.
MAO Inhibitors and Adrenergic Neuron Blockers	C	↓ sympathetic activity	Closely monitor patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine). The added ß-adrenergic blockade of metoprolol may excessively reduce sympathetic activity. Metoprolol

Metoprolol	Ref	Effect	Clinical comment
			tartrate should not be combined with other ß-blockers.
Nitroglycerin	C	↑ hypotensive effect of metoprolol tartrate	Nitroglycerin may enhance the hypotensive effect of metoprolol tartrate.
NSAIDs	C	↓ antihypertensive effect of ß-blockers	Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker may decrease the antihypertensive effect of ß-blockers, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by non-steroidal anti-inflammatory drugs.
Oral Antidiabetics drugs and insulin	C	↑ blood pressure associated with severe bradycardia	ß-blockers may interfere with the usual hemodynamic response to hypoglycemia and produce a rise in blood pressure associated with severe bradycardia. The dosage of oral antidiabetics may have to be readjusted in patients receiving β-blockers (see ***Warnings and Precautions***).
Prazosin (selective alpha-1-adrenergic antagonist)	C	↑ acute postural hypotension	The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a ß-blocker, including metoprolol tartrate.
Sympathomimetics	C	hypertension	Concomitant administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including antitussives or nose and eye drops) with a ß-blocker may enhance the pressor response resulting in hypertension due to mutual inhibition of therapeutic effects.
Aldesleukin or other drugs known to decrease blood pressure	T	↑ hypotensive effect of metoprolol tartrate	Concomitant administration of beta-blockers with other drugs known to decrease blood pressure such as aldesleukin may result in an enhanced hypotensive effect.

Drug-Food Interactions

Food enhances the bioavailability of an oral dose of metoprolol by approximately 20-40%. Indeed, food intake affects the pharmacokinetics of metoprolol leading to increased exposure (AUC) and a higher maximum plasma concentration (Cmax) (see ***Action and Clinical Pharmacology***). Hence, in order to minimize the effect variations within the individual, it is recommended that the drug should be administered with or immediately following meals.

In one clinical study with metoprolol immediate release formulation, it was found that Cmax and AUC were higher by about 32% and 38%, respectively, when administered after standard breakfast as compared to fasting condition. The study recommended that the drug should be administered with or immediately following meals to minimize the variations within an individual.

Drug-Herb Interactions

The interaction of metoprolol with herbal medications or supplements has not been studied.

Drug-Laboratory Interactions

No data suggest that metoprolol interferes with laboratory tests.

Drug-Lifestyle Interactions

Dizziness, fatigue or visual impairment may occur during treatment with metoprolol tartrate (see **Adverse Drug Reactions**) and may adversely affect the patient's ability to drive or use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Myocardial Infarction

In addition to the usual contraindications:

ONLY PATIENTS WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION WHO MEET THE FOLLOWING CRITERIA ARE SUITABLE FOR THERAPY AS DESCRIBED BELOW:	
Systolic Blood Pressure	≥ 100 mmHg
Heart Rate *	≥ 45 beats per minute
PR Interval	< 0.24 seconds
Rales*	< 10 cm
Adequate peripheral circulation	

*Extreme caution should be exercised when giving intravenous metoprolol to patients with heart rate between 45 and 60 and/or pulmonary rales less than 10 cm.

Therapy should be discontinued in patients if the heart rate drops below 45 or the systolic blood pressure drops below 100 mmHg.

Early Treatment

During the early phase of definite or suspected acute myocardial infarction, treatment with Metoprolol Tartrate Injection USP can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of Metoprolol Tartrate Injection USP each. The injections should be given at approximately 2-minute intervals. During the intravenous administration of Metoprolol Tartrate Injection USP, blood

pressure, heart rate, and electrocardiogram should be carefully monitored. If any of the injections are associated with adverse cardiovascular effects, intravenous administration should be stopped immediately and the patient should be observed carefully and appropriate therapy instituted.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets*, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily ***(see Late Treatment*** below).

Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg* every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol tartrate should be discontinued (***see Warnings and Precautions***).

Late Treatment (For proven myocardial infarction patients only)

Patients with contraindications to treatment during the early phase of myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets*, 100 mg twice daily, as soon as their clinical condition allows. Treatment can begin within 3-10 days of the acute event. Therapy should be continued for at least 3 months. Although the efficacy of treatment with metoprolol tartrate beyond 6 months has not been conclusively established data from studies with other ß-blockers suggest that the treatment should be continued for 1-3 years.

Special populations

Pediatric patients

No pediatric studies have been performed. The safety and efficacy metoprolol tartrate in pediatric patients have not been established.

* Metoprolol tartrate tablets are not marketed by SteriMax Inc. Therefore, when metoprolol tartrate tablets are recommended, a Product Monograph for metoprolol tartrate tablets should be consulted.

Renal impairment

No dose adjustment of metoprolol tartrate is required in patients with mild to moderate renal impairment. Caution and regular monitoring of renal function are required in patients with severe renal impairment (see ***Actions and Clinical Pharmacology - Pharmacokinetics - Special populations***).

Hepatic impairment

Metoprolol tartrate blood levels are likely to increase substantially in patients with mild to moderate hepatic impairment. Therefore, metoprolol tartrate should be initiated at low doses with cautious gradual dose titration according to clinical response and safety monitoring. Patients with severe hepatic impairment should be treated with caution i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs (see ***Actions and Clinical Pharmacology - Pharmacokinetics - Special populations***).

Geriatric patients (>65 years)

Metoprolol tartrate should be given with caution in geriatric patients due to increased likelihood of adverse events. Lower starting and maintenance doses and safety monitoring are recommended (see ***Actions and Clinical Pharmacology - Pharmacokinetics - Special populations***).

OVERDOSAGE

Symptoms

The most common signs to be expected with overdosage of a ß-adrenoreceptor agent are hypotension, bradycardia, congestive heart failure, myocardial infarction, bronchospasm and hypoglycemia. Atrioventricular block, cardiogenic shock and cardiac arrest may develop. In addition, impairment of consciousness (or even coma), convulsions, nausea, vomiting and cyanosis and death may occur.

Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravate the signs and symptoms.

The first manifestations of overdosage set in 20 minutes to 2 hours after drug administration.

Management

If overdosage occurs, in all cases, therapy with metoprolol tartrate should be discontinued, the patient hospitalized and observed closely.

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Bradycardia and Hypotension: Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, norepinephrine or dopamine may be administered after preceding treatment with atropine. (***See Precaution*** concerning the use of epinephrine in ß-blocked patients.) In case of hypoglycemia glucagon (1-10 mg) can be administered.

Heart Block (second- or third- degree): Isoproterenol or transvenous cardiac pacemaker.

1. Congestive Heart Failure: Conventional therapy.
2. Bronchospasm: Intravenous aminophylline or a b_2-agonist.
3. Hypoglycemia: Intravenous glucose.

It should be remembered that metoprolol tartrate is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of metoprolol tartrate. However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Metoprolol tartrate is a ß-adrenergic receptor-blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on the b_1-adrenoreceptors, chiefly located in cardiac muscle. This

preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits β_2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. metoprolol tartrate has no membrane-stabilizing or partial agonism (intrinsic sympathomimetic) activities. It is used in the treatment of hypertension, angina pectoris and to reduce mortality in patients with myocardial infarction.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

a) Competitive ability to antagonize catecholamine-induced tachycardia at the b-receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output;
b) Inhibition of renin release by the kidneys;
c) Inhibition of the vasomotor centres.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort. However, in patients with heart failure, ß-adrenergic receptor blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure (preload).

The mechanisms involved in reducing mortality in patients with acute myocardial infarction are not fully understood.

Pharmacodynamics

Significant ß-blocking effect (as measured by reduction of exercise heart rate) occurs within one 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.

Pharmacokinetic and pharmacodynamic relationship

Following intravenous administration of metoprolol tartrate, the half-life of the distribution phase is approximately 12 minutes; the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum ß-blockade was achieved at

approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal ß-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 metoprolol tartrate 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.

Pharmacokinetics

The drug is available in racemic form and it exhibits stereo-specific pharmacokinetics.

Absorption: In humans, following oral administration of conventional tablet, metoprolol is rapidly and almost completely absorbed from the gastrointestinal tract. The drug is absorbed evenly throughout gastrointestinal tract. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Distribution: Metoprolol is rapidly and extensively distributed to the extra-vascular tissue. The mean volume of distribution is 3.2 to 5.6 L/kg. The apparent volume of distribution at steady-state (Vss) in extensive metabolizers (4.84 L/kg) is almost 2-fold higher than of poor metabolizers (2.83 L/kg). At therapeutic concentrations, approximately 12 % of metoprolol tartrate is bound to human serum

proteins. Metoprolol crosses the placenta and is found in breast milk (see Warnings and ***Precautions - Nursing Women***).

Biotransformation / Metabolism: Metoprolol is not a significant P-glycoprotein substrate but is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6), which causes inter-individual variability in pharmacokinetics and pharmacodynamics of metoprolol.

Indeed, the accumulation of metoprolol leads to high levels of the drug in plasma in poor metabolizers (PMs), which are associated with higher intensity of therapeutic effects, an increase in duration of action and an increase in the occurrence and severity of AEs as compared to extensive metabolizers (EMs).

Metabolism & Dose-proportionality: Metoprolol exhibits saturable pre-systemic metabolism leading to non-proportionate increase in exposure with increased dose.
Food enhances the bioavailability of an oral dose of metoprolol by approximately 20-40%. Indeed, food intake affects the pharmacokinetics of metoprolol leading to increased exposure (AUC) and a higher maximum plasma concentration (Cmax) (see ***Drug Interactions - Drug Food Interactions***).

In one clinical study with metoprolol immediate release formulation, it was found that Cmax and AUC were higher by about 32% and 38%, respectively, when administered after standard breakfast as compared to fasting condition. The study recommended that the drug should be administered with or immediately following meals to minimize the variations within an individual.

Elimination: Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 hours (range: 1 [in EMs] to 9 hours [in PMs]). The total clearance rate of an intravenous dose is approximately 1L/min and the protein binding rate is approximately 10%.
Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following single oral administration of 100 mg metoprolol the median clearance were 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultrarapid metabolizers, respectively.

Special Populations and Conditions

Elderly: The elderly population show higher plasma concentrations of metoprolol (up to 28% AUC increase in elderly patients as compared to young healthy volunteers) as a combined result of a decreased elimination of metoprolol and the metabolite α-hydroxy-metoprolol and a decreased hepatic blood flow due to age-related physiological changes. In addition, time to reach peak concentration, Tmax, was significantly longer in the elderly population. Hence, it is recommended to initiate therapy with lower doses in this group and safety monitoring may be recommended.

Ethnic sensitivity: The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Orientals are PMs. CYP2D6 poor metabolizers exhibit 5-fold higher plasma concentrations of metoprolol than extensive metabolizers with normal CYP2D6 activity.

Hepatic impairment: Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment impacts the pharmacokinetics of metoprolol. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h), in patients with liver impairment. Hence, dose adjustment and safety monitoring are advised in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should be treated with caution, i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs.

Renal impairment: Pharmacokinetics of metoprolol in patient with renal impairment did not differ to a clinically significant degree from normal subjects. However, there is accumulation of one of its less active metabolite in patients with a creatinine clearance below 5 mL/min. Since the resulting metabolite accumulation has no significant effect on the ß-blocking effects, metoprolol dosing does not need to be altered in patient with mild to moderate renal impairment. Caution is advised in the use of a beta-blocker in patients with severe renal impairment and safety monitoring is advised in these patients.

STORAGE AND STABILITY

Store Metoprolol Tartrate Injection USP at 15°C -30°C. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Metoprolol Tartrate Injection USP is for single use only. All parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Discard any unused portion or solution with particulate matter or discoloration.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Metoprolol Tartrate Injection USP is a clear and colorless sterile solution for injection.

Metoprolol Tartrate Injection USP is available in 5 mL vials as a 1 mg/mL strength solution.

Each mL of Metoprolol Tartrate Injection USP contains 1 mg of metoprolol tartrate, 9 mg of sodium chloride, and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

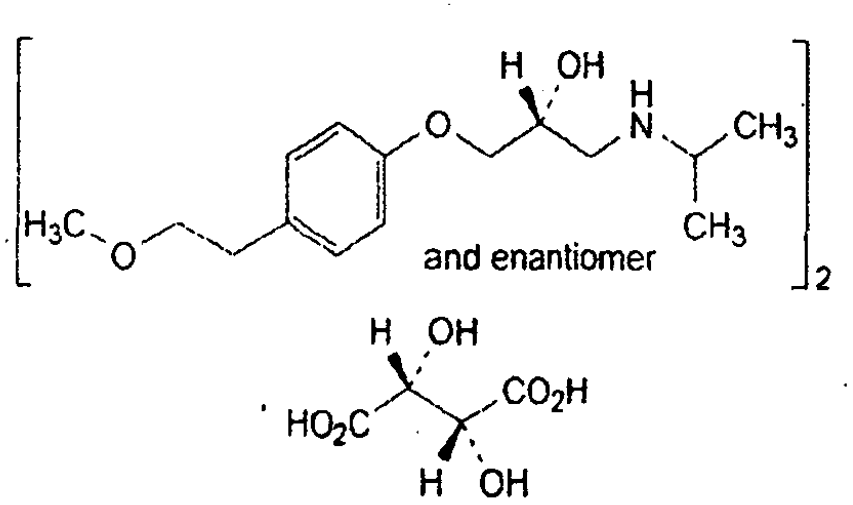
Drug Substance

Proper name: Metoprolol tartrate

Chemical name: 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (±)-, [*R*- (*R**,*R**)]-2,3-dihydroxybutanedioate (2:1) (salt)

Molecular formula and molecular mass: $(C_{15}H_{25}NO_3)_2 \bullet C_4H_6O_6$; 684.81

Structural formula:



Physicochemical properties: White, crystalline powder. Very soluble in water, freely soluble in Methylene Chloride, in Chloroform, and in Alcohol; slightly soluble in Acetone; insoluble in Ether. pH is between 6.0 and 7.0. Melting point is 120˚C.

DETAILED PHARMACOLOGY

Effect on the Cardiovascular System

Metoprolol produced dose-dependent reductions in heart rate and contractile force responses to sympathetic nerve stimulation in the anaesthetized cat. The ED_{50} 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 anaesthetized cats, intravenous doses up to 2.0 mg/kg did not significantly influence the pressor response to intravenous epinephrine.

In anaesthetized cats, intravenously-administered metoprolol antagonized the hind limb vasodilating response to intra-arterial isoproterenol in much higher doses (ED_{50} 5 mg/kg) than required to block the increase in chronotropic response (ED_{50} 0.4 mg/kg) or increase in contractile force (ED_{50} 0.2 mg/kg).

In 5 healthy volunteers, intravenously-administered 10 mg doses of metoprolol reduced exercise induced tachycardia by 13% and systolic blood pressure during exercise by 13%. The decrease in mean blood pressure after epinephrine was abolished by metoprolol, whereas the increase in systolic blood pressure was reduced by 50%; vascular resistance in the forearm was unchanged after metoprolol.

In healthy volunteers, intravenous metoprolol 0.15 mg/kg significantly lowered cardiac output by 1.3 litre/min. at rest, and 3.6 litre/min. during exercise. The mean decreases in heart rate were 9 and 16 beats/min. during rest and exercise, respectively. Right atrial pressure was significantly increased during rest and exercise. Oxygen consumption was not significantly influenced by drug administration. Significant increases in the calculated arteriovenous oxygen differences were observed (6 and 20 mL/litre at rest and during exercise, respectively).

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.

A single oral dose of 40 mg of metoprolol administered to 17 anginal patients 90 minutes before testing, increased total work performed from 5994 to 8462 k.p.m. (40%). Times to onset of pain and appearance of ST depression were similarly increased from 11.8 to 16.9 minutes and 9.9 to 13.9 minutes respectively.

Effects on Pulmonary Function

The effects on specific airways resistance (SRaw) of single oral doses of 100 mg of metoprolol were assessed in 6 healthy volunteers and in 12 patients with bronchial asthma. No bronchodilator was used. Metoprolol did not have a significant effect on SRaw in the normal subjects, but in the asthmatic patients, SRaw was significantly increased. Similar findings were observed with an 80 mg dose of propranolol.

In a controlled study, 17 patients with bronchial asthma received concomitantly a bronchodilator (terbutaline) with 50 or 100 mg b.i.d. of metoprolol. The FEV1 values fell only in the high dose group, indicating some b_2-blocking effect.

Other Effects

Metoprolol showed a negligible local anaesthetic effect on the isolated sciatic nerve of the frog and in the intracutaneous wheal test in guinea pigs. The cardiostimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg 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.

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.

TOXICOLOGY

Acute Toxicity

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

The toxic symptoms in rats include: sedation, ataxia, piloerection, irritation, spasm, and lacrimation. Rats were unconscious before death, which occurred within 5-10 minutes after intravenous injection 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. No symptoms of toxicity were detectable 24 hours after administration in surviving animals.

Long-Term Toxicity (Subacute)

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rats	4	10 M 10 F	Saline, 10, 50, 100/day (after 14 days, high dose increased to 200/day)	P. O.	5 Wks	Slight increase in hematocrit and slight decrease in blood sugar in high-dose females.
Beagle Dogs	1	1 M 1 F	40 x 3 days, increased by 20/day to 140 x 6 days to 160/day.	P. O.	3 Wks	Disturbance of balance; increased abdominal muscular tone, mydriasis, hyperemia in visible mucouse membranes. One dog died at dose level of 140 mg/kg/day.
Beagle Dogs	2	1 M	80 b.i.d. one day; 2 days	P. O.	3 Days	Disturbance of balance;

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
			later, single dose of 100.			vomiting, prostration, dyspnea, loss of consciousness, death.
		2 F	20 b.i.d. inceased evey 5 days by 20 b.i.d. up to 120 b.i.d.	P.O.	4 Wks	Vomiting; increased salivation, tremor, ataxia. One dog died at highest dose.
Beagle Dogs	4	1 M 1 F	0, 5, 20, 40/day	P. O.	4 Wks	None.
Beagle Dogs	3	1 M 1 F	Saline, 0.5, 5/day	I. V.	2 Wks	Prolonged PR interval in ECG.
Beagle Dogs	2	1 M 1 F	Saline, 5 /day	I. V.	2 Wks	Prolonged PR interval in ECG.

Long-Term Toxicity (Chronic)

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rats	4	15 M 15 F	Saline, 10, 100, 200/day. High dose increased to 200/day after 13 Weeks	P. O.	6 months	None
Beagle Dogs	One Control	2 M 2 F	0, 5, 20, 40 b.i.d. After 7 weeks, high dose increased to 50/b.i.d. After 3 months, intermediate dose increased to 30 b.i.d. and high dose to 80 b.i.d.	P. O.	6 months	Bradycardia, increased PR interval and QT interval in ECG.
	Three Active	3 M 3 F				
Beagle Dog	One Control	6 M 6 F	0, 10, 60 day. High level dogs received 120 on day 1, 60 on days 3 to 8; 90/day on days 9 to 22 and 105/day for balance.	P. O.	1 Year	2 high-dose dogs died on day 1, otherwise, none.
	Three Active	6 M 6 F				

Teratology and Reproduction Studies

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 20 pregnant rats on days 6-15 of gestation. Treatment with metoprolol did not adversely affect any of the parameters studied.

Rabbit: (New Zealand White strain) Doses of 5, 12.5 and 25 mg/kg were administered orally to groups of 20 pregnant 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.

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 50 rats from day 15 of gestation, through lactation to 21 days postpartum. Parameters studied in litter and parent animals were not adversely affected.

Rat: (Charles River CD strain) Doses of 50 and 500 mg/kg were administered orally to groups of 10 male and 20 female 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 postpartum, with an interim sacrifice at day 13 of gestation. The only significant finding in this study was a slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day and a higher frequency of stillbirths in the high dose group.

Carcinogenicity Studies

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 received 2-AAF (positive control) 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 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 per day for 78 weeks showed that the tumors were distributed with equal frequency in the treated and control groups.
The strain was susceptible to the known carcinogen.

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PART III: CONSUMER INFORMATION

[Pr]Metoprolol Tartrate Injection USP
5 mg / 5 mL (1 mg / mL)

This leaflet is part III of a three-part "Product Monograph" published when Metoprolol Tartrate Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Metoprolol Tartrate Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Metoprolol Tartrate Injection USP is used alone or in combination with another medicine for the following conditions:

- To help to protect the heart after a heart attack (myocardial infarction)

What it does:
Metoprolol Tartrate Injection USP is a beta-blocker. It helps to control heart-related problems.

When it should not be used:
You should not be treated with Metoprolol Tartrate Injection USP if you:

- are allergic to metoprolol, to any of the other ingredients in Metoprolol Tartrate Injection USP or to another beta-blocker
- have breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of a heart disorder)
- have a slow or irregular heartbeat
- have sudden and oppressive chest pain (sign of heart attack)
- have very poor blood circulation in your limbs (for example, very cold, pale hands or feet, or pain in your leg muscles when you walk)
- have low blood pressure
- have non-treated tumor of the medulla of the adrenal glands (pheochromocytoma)
- have asthma or had history of difficulty breathing with wheezing or coughing
- have severe skin problems
- suffer from severe drop in blood pressure, dizziness, fast heartbeat, rapid and shallow breathing, cold clammy skin (signs of a heart disorder named cardiogenic shock)

What the medicinal ingredient is:
Metoprolol tartrate.

What the nonmedicinal ingredients are:
Metoprolol Tartrate Injection USP contains sodium chloride and water for injection.

What dosage forms it comes in:
Metoprolol Tartrate Injection USP is available as a 1 mg/mL solution in single-use glass vials.

WARNINGS AND PRECAUTIONS

BEFORE you use Metoprolol Tartrate Injection USP talk to your doctor or pharmacist if you:

- have heart, liver or kidney disease
- have high or low levels of sugar in the blood (diabetes)
- are at risk for serious allergic reactions
- have chest pain when you are at rest
- have poor blood circulation in your limbs (for example, very cold, pale hands or feet, or pain in your leg muscles when you walk)
- have a tumor of the medulla or of the adrenal glands (pheochromocytoma), you would require an additional treatment to metoprolol tartrate
- have an overactive thyroid gland
- have respiratory disease such as asthma, or sometimes get breathlessness and wheezing
- have a severe syndrome named oculomucocutaneous syndrome whose signs include severe conjunctivitis (red, irritated and watery eye), skin rash and ear infection
- are pregnant, or intend to become pregnantMetoprolol Tartrate should not be used during pregnancy. Your doctor will discuss with you the potential risks of taking metoprolol tartrate during pregnancy
- are breast feeding. If your doctor decides that you must continue to take metoprolol tartrate you should stop breastfeeding as metoprolol tartrate passes into breast milk
- are under 18 years old

If you need to undergo an operation where an anesthetic is used, tell your anesthetic professional that you are taking metoprolol tartrate.

Driving and using machines: If you experience dizziness, tiredness or blurred vision during your treatment with metoprolol tartrate, do not drive, use machinery, or perform other tasks that need full attention until you know how you respond to metoprolol tartrate. Drinking alcohol may increase tiredness.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have

recently taken any other medicines, including herbal and non-prescription medicines. Some other medicines may interact with metoprolol tartrate. These include:

- medicines used to treat high blood pressure,
- medicines used to treat chest pain (angina) (e.g. nitroglycerin),
- medicines used to treat irregular heartbeat (e.g. amiodarone, propafenone, quinidine, disopyramidetocainide, procainamide, ajmalineamiodarone, flecainide, digitalis glycosides such as digoxin, lidocaine),
- anaesthetics, medicines used during surgical operations,
- adrenaline or similar substances (sympathomimetics), which are found in some eye and nose drops, and in some cough medicines or remedies for the common cold (e.g. noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives),
- insulin, or medicines used to treat high levels of sugar in the blood (diabetes),
- medicines used to relieve pain or inflammation (nonsteroidal anti-inflammatory drugs such as COX-2 inhibitors),
- antibiotics (e.g. rifampicin),
- antivirals (e.g. ritonavir),
- antihistamines used to treat hay fever (e.g. diphenhydramine),
- medicines used to treat malaria (e.g. hydroxychloroquineor quinine),
- antipsychotic medicines (e.g. thioridazine, chlorpromazine, fluphenazine, haloperidol),
- antidepressants (e.g. fluoxetine, paroxetine, fluvoxamine, sertraline, clomipramine, desipramine or bupropion),
- MOA Inhibitors and adrenergic neuron blockers (e.g. reserpine or guanethidine),
- antifungals (e.g. terbinafine),
- ergot alkaloids, used in the prevention and treatment of migraine headaches,
- dipyridamole, used to reduce the risk of blood clots,
- alcohol,
- fingolimod, a medicine used to treat multiple sclerosis
- Aldesleukin, a medicine used to treat kidney cancer, or other medicines that may cause a decrease in blood pressure

PROPER USE OF THIS MEDICATION

Usual dose:
Follow your doctor's instructions carefully. Do not exceed the recommended dosage.

Metoprolol Tartrate Injection USP is used for the emergency treatment of heart attacks. It is only used by an experienced health care provider under circumstances where resuscitation and monitoring equipment is available.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Some of the effects of an overdose of metoprolol tartrate are: an abnormally slow heartbeat or an irregular heartbeat, very low blood pressure, breathlessness, difficulty breathing when lying down, swelling of the feet, loss of consciousness, blue discoloration of the lips, tongue, skin, seizures, nausea and vomiting, sudden and oppressive chest pain and death.

Missed Dose:
Contact your physician immediately for further instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, metoprolol tartrate **may cause some side effects. These side effects may be minor and temporary. However, some may be serious and need medical attention.**

Side effects may include: sleep disturbance, fatigue and tiredness especially with activity, headache, dry mouth, nausea and vomiting, diarrhea or constipation and abdominal pain, numbness, a tingling sensation in the extremities signs of paresthesia, increased sensitivity of the skin to sun, sweating, hair loss, increased weight, and lower back pain.

Based on your health history, your doctor should take blood tests for as long as you are being treated with metoprolol tartrate.
They may monitor:

- blood sugar
- heart, liver, kidney and thyroid function
- how metoprolol tartrate is affecting other medications that you are taking.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk to your doctor or pharmacist		Stop taking drug and immediately seek assistance
		Only if severe	In all cases	
Common	**Low Blood Pressure**: feeling of lightheadedness or fainting especially when getting up from a lying or sitting position		✓	
	Chest Pain		✓	
	Bronchospasm: difficulty breathing with wheezing or coughing		✓	
	Heart Failure: shortness of breath, leg swelling and tiredness especially with activity			✓
Uncommon	**Edema:** ankle swelling	✓		
	Slow or irregular heartbeat (palpitations)		✓	
	New or Worsening Psoriasis: skin rash (in the form of itchy rash, thickened patches of red/silver skin)	✓		
	Allergic Reaction: rash, hives, swelling of the face, throat, lips, difficulty swallowing or breathing			✓
	Liver Disorder: yellowing of the skins or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			
	Sexuality: Abnormal curvature of the penis.	✓		
	Change in sex drive	✓		
	Change in ability to achieve or maintain an erection	✓		
	Hallucinations: see or hear things that are not there		✓	
	Depression: feel sad, loss of interest in usual activities changes in sleep and eating patterns		✓	
	Change in personality and confusion		✓	
	Visual Disturbance: Blurred vision, dry or irritated eyes	✓		
	Hearing Disturbance: noises, reduced or loss of hearing	✓		
	Parasthesia: Colder than usual hands or feet	✓		
	Gangrene: toes or fingers cold to the touch, discoloured and painful			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect	Talk to your doctor or pharmacist		Stop taking drug and immediately seek assistance
	Only if severe	In all cases	
Kidney Disorder: change in frequency of urination, swelling of extremities, fatigue, skin rash, itching, nausea, vomiting	✓		
High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.			✓
Decreased Platelets: bruising, bleeding, fatigue and weakness		✓	
Retroperitoneal fibrosis: lower back pain, kidney failure (low or no urine produced), high blood pressure, blood clot in the legs (See **Blood Clots** above)			✓
Arthritis: stiff sore joints		✓	
Oculomucocutaneous Syndrome: red, irritated and watery eyes, skin rash and ear infection			✓

This is not a complete list of side effects. For any unexpected effects while taking Metoprolol Tartrate Injection USP contact your doctor or pharmacist.

HOW TO STORE IT

Store vials between 15 ˚C - 30˚C. Protect from light.

Keep all medicines out of the reach and sight of children.

This medicine is prescribed for your specific medical problem and for your own use only. Do not give to other people.

Do not use outdated medicines. Discard them safely out of the reach of children or take them to your pharmacist who will dispose of them for you.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.sterimaxinc.com

or by contacting the sponsor, SteriMax Inc., at:

1-877-546-7667

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