Metoprolol tartrate

Cardiosel®

50 mg and 100 mg Tablet

BETA-ADRENOCEPTOR BLOCKER
ANTIHYPERTENSIVE
ANTI-ANGINAL

FORMULATION
Each tablet contains:
Metoprolol tartrate .....50 mg or 100 mg

PRODUCT DESCRIPTION:
Metoprolol tartrate (Cardiosel®) 50 mg Tablet: White, 1/4" diameter, round, biconvex tablet, plain on both sides
Metoprolol tartrate (Cardiosel®) 100 mg Tablet: White, 11/32" diameter, round, biconvex tablet, bisected on one side and plain on the other side

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Metoprolol is a beta-adrenergic receptor blocking agent which acts preferentially on beta$_1$ adrenoceptors, mainly located in cardiac muscle. This preferential effect is not absolute since at higher doses metoprolol also inhibits beta$_2$ adrenoceptors, mainly located in the bronchial and vascular musculature. Metoprolol has no partial agonist (intrinsic sympathomimetic) activity and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade.

Metoprolol's beta-blocking activity is manifested by (1) a decrease in heart rate and cardiac output at rest and upon exercise, (2) decrease in systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) decrease in reflex orthostatic tachycardia.

The antihypertensive mechanism of beta-blockers has not been elucidated. Several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (particularly cardiac) adrenergic neuron sites resulting in decreased cardiac output, (2) a central effect leading to decreased sympathetic outflow to the periphery, and (3) suppression of renin activity.

In angina pectoris, metoprolol decreases the frequency and severity of ischemic episodes and increases physical working capacity. These beneficial effects may be due to decreased myocardial oxygen demand as a result of the decreased heart rate and myocardial contractility.

In supraventricular tachycardia, atrial fibrillation, ventricular extrasystoles or other ventricular arrhythmias, metoprolol has a regulating effect on the heart rate. Its anti-arrhythmic effect is due to inhibition of automaticity of pacemaker cells and prolongation of atrioventricular (AV) conduction.

Metoprolol decreased mortality in patients with suspected or confirmed myocardial infarction. This effect is due to a decreased incidence of severe ventricular arrhythmias and limitation of infarct size. Metoprolol has also been shown to decrease the incidence of non-fatal myocardial reinfarction.

PHARMACOKINETICS
Metoprolol is readily and completely absorbed from the gastrointestinal tract. Peak plasma metoprolol concentrations are achieved 1.5 to 2 hours after dosing. Due to extensive hepatic first-pass metabolism, the bioavailability of a single metoprolol dose is about 50%, increasing to 70% during repeated administration. Ingestion with food may increase the bioavailability of a single oral dose by about 20 to 40%.

Metoprolol is widely distributed, with a volume of distribution of 3.2 to 5.6 L/kg. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 10% bound to plasma protein. Metoprolol levels in cerebrospinal fluid are similar to those in plasma in patients with hypertension.

Metoprolol is extensively metabolized in the liver, predominantly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, O-dealkylation followed by oxidation, and aliphatic hydroxylation. There are marked ethnic differences in the prevalence of poor metabolizers phenotype. About 7% of Caucasians and less than 1% Orientals are poor metabolizers. CYP2D6 poor metabolizers exhibit several-fold higher plasma metoprolol concentrations than extensive metabolizers with normal CYP2D6 activity. However, the CYP2D6 dependent metabolism of metoprolol appears to have little or no effect on its safety or tolerability.

Metoprolol and its inactive metabolites are excreted in urine mainly via glomerular filtration, although tubular secretion and reabsorption may be involved. Metoprolol's average elimination half-life is 3 to 4 hours; it may be 7 to 9 hours in poor metabolizers. About 95% of the dose can be recovered in urine within 72 hours. Less than 5% of an oral metoprolol dose is excreted unchanged in urine.

The excretion of metabolites is decreased in patients with renal impairment. Significant accumulation of metabolites will occur only in patients with creatinine clearance of about 5 mL /min or less, and this accumulation would not influence metoprolol's beta-blocking properties.

Liver cirrhosis may increase the bioavailability of unchanged metoprolol and decrease its total clearance.

Inflammatory disease has no effect on metoprolol's pharmacokinetics. Hyperthyroidism may increase presystemic metoprolol clearance.

INDICATIONS
- ***Hypertension:*** As monotherapy or in combination with other antihypertensive agents
- ***Angina pectoris:*** Long-term prophylaxis
- ***Cardiac arrhythmias:*** Disturbances of cardiac rhythm, including supraventricular and ventricular arrhythmias
- ***Myocardial infarction (MI):*** Treatment of hemodynamically stable patients with definite or suspected acute MI to reduce cardiovascular mortality
- Adjunct to treatment of thyrotoxicosis
- Prevention of migraine

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:
- Patients should regularly and continuously take metoprolol, as directed, with or immediately after meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it)
- Individualize dosage according to patient's clinical response.

INDICATION	RECOMMENDED ORAL METOPROLOL DOSE
Hypertension	**Usual Initial Adult Dose:** 50 to 100 mg daily given in single or divided doses ⇒ Dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. ⇒ Maximum effect in any given dosage level will be apparent after 1 week of treatment. ⇒ Effective Dosage Range: 100 to 450 mg daily
Angina pectoris	**Usual Initial Adult Dose:** 100 mg daily given in 2 divided doses ⇒ Dosage may be increased at weekly intervals until optimum control of angina is obtained or there is pronounced slowing of heart rate. ⇒ Effective Dosage Range: 100 to 400 mg daily ⇒ Gradually reduce dosage over a period of 1 to 2 weeks if metoprolol is to be discontinued.
Cardiac arrhythmias	**Usual Dose:** 100 to 150 mg daily given in 2 or 3 divided doses ⇒ Dose may be increased up to 300 mg daily given in divided doses
Myocardial infarction	**Early Treatment:** Begin with the intravenous (IV) administration of metoprolol. ⇒ ***In patients who tolerate the full IV dose,*** administer Metoprolol orally 15 minutes after the last IV dose at a dosage of **50 mg every 6 hours for 48 hours.** Thereafter, administer an oral maintenance dosage of **100 mg twice daily (see Late Treatment).** ⇒ ***In patients who appear not to tolerate the full IV dose,*** administer Metoprolol orally **25 or 50mg every 6 hours** 15 minutes after the last IV dose or as soon as their clinical condition permits. ⇒ ***In patients with severe intolerance,*** discontinue metoprolol treatment. **Late Treatment:** To reduce the risk of cardiovascular mortality in patients (1) with contraindications to treatment during the early phase of suspected or definite MI, (2) who appear not to tolerate the full early treatment, or (3) in whom therapy is delayed for any other reason should be started on oral metoprolol **100 mg twice daily**, as soon as their clinical condition permits. ⇒ Therapy should be continued for at least 3 months
Adjunct to treatment of thyrotoxicosis	**Usual Dose:** 150 to 200 mg (may be increased up to 400 mg) daily given in 3 or 4 divided doses
Prevention of migraine	**Usual Dose:** 100 mg daily given as a single dose in the morning ⇒ If necessary, dose may be increased to 200 mg daily given in 2 divided doses (morning and evening).
Or, as prescribed by a physician.	

CONTRAINDICATIONS
- Hypersensitivity to metoprolol or any other beta-blocker or any component of the product
- Hypertensive and angina patients with the following conditions:
  - Sinus bradycardia
  - Heart block greater than first degree
  - Cardiogenic shock
  - Overt or decompensated cardiac failure
  - Sick sinus syndrome
  - Severe peripheral arterial circulatory disorders
  - Pheochromocytoma
- Patient with acute myocardial infarction who have following conditions:
  - Heart rate < 45 beats/minute
  - Second- and third-degree heart block
  - Significant first degree heart block (P-R interval ≥ 0.24 sec)
  - Systolic blood pressure < 100 mmHg
  - Moderate to severe cardiac failure
- Patients with severe bronchial asthma or history of severe bronchospasm

WARNINGS AND PRECAUTIONS
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure. Cautiously administer metoprolol in hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics. Both digitalis and metoprolol slow AV conduction. Carefully monitor the hemodynamic status of the patient during metoprolol treatment. Discontinue metoprolol if heart failure occurs or persists despite appropriate treatment.

Hypertension and Angina
In Patients without a History of Cardiac Failure: Cardiac failure may result from prolonged depression of myocardium with beta-blockers over a period of time. Fully digitalize and/or give patient a diuretic at the first sign or symptom of impending cardiac failure (e.g., weight gain, increasing shortness of breath). If cardiac failure continues, discontinue metoprolol, gradually if possible.

Ischemic Heart Disease: **Exacerbations of angina pectoris, and in some cases, myocardial infarction have occurred after abrupt discontinuation of certain beta-blockers. Gradually reduce dosage over a period of 1 to 2 weeks and carefully monitor the patient when discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease. Metoprolol should promptly be reinstated, at least temporarily, and initiate other measures appropriate for the management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Patients should be warned against interruption or discontinuation of therapy without physician's advice. It may be prudent not to discontinue metoprolol abruptly even in patients treated only for hypertension since coronary artery disease is common and may be unrecognized.**

Bronchospastic Diseases: **IN GENERAL, PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD NOT RECEIVE BETA-BLOCKERS, INCLUDING METOPROLOL. Because of its relative beta$_1$ selectivity, however, metoprolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, coadminister a beta$_2$-stimulating agent, and use the lowest possible metoprolol dose. In these cases it would be prudent initially to give metoprolol in smaller doses thrice daily, instead of larger doses twice daily, to avoid higher plasma levels associated with longer dosing intervals.**

Major Surgery: **The necessity or desirability of withdrawing beta-blockers, including metoprolol, prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may increase the risks of general anesthesia and surgical procedures.**

Like other beta-blockers, metoprolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents (e.g., dobutamine or isoproterenol). However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been observed with beta-blockers.

Diabetes and Hypoglycemia: **Use with caution in patients with diabetes mellitus, particularly those who are receiving insulin or oral hypoglycemic agents. Diabetic patients should be warned that beta-blockers, including metoprolol, may mask the tachycardia occurring with hypoglycemia; however, other manifestations of hypoglycemia such as dizziness and sweating may not be significantly affected.**

Pheochromocytoma: **Metoprolol is contraindicated in patients known to have, or suspected of having, a pheochromocytoma. Metoprolol should always be given in combination with an alpha-blocker, and only after the alpha-blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.**

Thyrotoxicosis: **Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Carefully manage patients suspected of developing thyrotoxicosis to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.**

Myocardial Infarction
Bradycardia: Metoprolol decreases sinus heart rate in most patients. This decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction, particularly inferior infarction, may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, administer atropine 0.25 to 0.5 mg intravenously. Discontinue metoprolol if treatment with atropine is not successful, and consider cautious administration of isoproterenol or installation of a cardiac pacemaker.

AV Block: Metoprolol slows AV conduction and may produce significant first-(P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Similarly, acute myocardial infarction produces heart block.

Discontinue metoprolol and administer atropine 0.25 to 0.5 mg intravenously if heart block occurs. Consider cautious administration of isoproterenol or installation of a cardiac pacemaker if treatment with atropine is not successful.

Hypotension: Discontinue metoprolol if hypotension (systolic blood pressure ≤ 90 mmHg) occurs and carefully assess the hemodynamic status of the patient and the extent of myocardial damage. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Institute appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these.

Bronchospastic Diseases (see **also Boxed Warning**): **Because it is not known to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. Discontinue metoprolol if bronchospasm not related to congestive heart failure occurs. Administer cautiously a theophylline derivative or a beta$_2$-agonist, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$-agonists may produce serious cardiac arrhythmias.**

General

- Use with caution in patients with impaired hepatic failure.
- Patients should be advised (1) to avoid operating machinery or engaging in other tasks requiring alertness until the patient's response to metoprolol therapy has been determined, (2) to contact the physician if any difficulty in breathing occurs, and (3) to inform the physician/dentist before any type of surgery that he or she is taking metoprolol.
- While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
- The full oculomucocutaneous syndrome has not been observed with metoprolol; however, part of this syndrome (dry eyes either alone or, occasionally, with skin rashes) has occurred. In most cases, symptoms cleared upon discontinuation of metoprolol. Carefully observe patients for potential ocular effects. If such effects occur, metoprolol should be discontinued.

INTERACTIONS WITH OTHER MEDICAMENTS
Catecholamine-depleting drugs (e.g., reserpine): Additive effect when given with beta-blockers. Patients given these drugs should be observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Calcium channel blockers (e.g., verapamil, diltiazem): May potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and AV conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients taking metoprolol due to the risk of cardiac arrest in this situation. Closely monitor patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol.
Class I Anti-arrhythmic drugs and Amiodarone: Amiodarone, propafenone, and other class I anti-arrhythmic agents (e.g., quinidine, disopyramide) may potentiate the effects of beta-blockers on heart rate and AV conduction.
Clonidine: If a patient is treated concurrently with clonidine and metoprolol, and clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine. This is because the hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.
CYP2D6 inhibitors: Potent inhibitors of this enzyme may increase plasma metoprolol concentration. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer. Thus, use with caution when coadministering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants (e.g., fluoxetine, paroxetine, bupropion), antipsychotics (e.g., thioridazine), antiarrhythmics (e.g., quinidine, propafenone), antiretrovirals (e.g., ritonavir), antihistamines (e.g., diphenhydramine), antimalarials (e.g., hydroxychloroquine, quinidine), antifungals (e.g., terbinafine), and medications for stomach ulcers (e.g., cimetidine).
Digitalis glycosides: Concomitant use may result in excessive bradycardia and/or increase in AV conduction time
General anesthetics: Some inhalation anesthetics may enhance the cardiopressant effect of beta-blockers
Hepatic enzyme inducers/inhibitors: Enzyme inducing agents (e.g., rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g., cimetidine) may increase plasma metoprolol concentrations.
Insulin and oral hypoglycemic drugs: Beta-blockers may be associated with increased or prolonged hypoglycemia in diabetic patients who use insulin. Beta-blockers may also antagonize the hypoglycemic effects of sulfonylureas. The risk of either effect is less with a beta$_1$-selective drug such as metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.
Lidocaine (xylocaine): Metoprolol may reduce the clearance of lidocaine, leading to increased lidocaine effects.
Nitroglycerin: May enhance metoprolol's hypotensive effect
Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., indomethacin): May decrease metoprolol's antihypertensive effect
Prazosin: The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker.
Sympathomimetics: Metoprolol will antagonize the beta$_1$ effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta$_2$-agonists at normal therapeutic doses.
Alcohol: During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly.
Other drugs:
- ***Other antihypertensive drugs:*** Additive effect; care should be taken to avoid hypotension. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.
- As beta-blockers may affect the peripheral circulation, exercise caution when drugs with similar activity (e.g., ergotamine) are given concurrently.
- Use with caution when beta-blockers are coadministered with sympathetic ganglion blocking agents, other beta blockers (including in form of eye drops), or monoamine oxidase (MAO) inhibitors.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category C. Although there are no adequate and controlled studies to date in humans, metoprolol has been shown to increase post-implantation loss and to decrease neonatal survival in rats when given at metoprolol tartrate dosages up to 55.5 times the maximum recommended human dosage of 450 mg daily. Metoprolol should be used in pregnancy only if clearly needed.

Lactation: Since metoprolol is distributed into milk, the drug should be used with caution in breastfeeding mothers.

Geriatrics: There were no age-related differences in safety and efficacy.

Children: The safety and efficacy in children have not been established.

UNDESIRABLE EFFECTS
Cardiovascular: Arterial insufficiency (e.g., Raynaud's phenomenon), bradycardia, cold extremities, cardiac arrhythmias, cardiac conduction disorders, chest pain, claudication, congestive heart failure, decreased high-density lipoprotein (HDL), edema, first-degree heart block, gangrene in patients with pre-existing severe peripheral circulatory disorders (rare), hypotension, increased triglycerides, orthostatic hypotension occasionally with syncope, palpitations, peripheral edema, precordial pain, second- or third-degree heart block
Endocrine/Metabolic: Decreased libido, hypoglycemia, unstable diabetes, weight gain; ***Increases in the following:*** alkaline phosphatase, transaminases, lactate dehydrogenase, blood urea nitrogen (BUN), serum creatinine, uric acid
Gastrointestinal: Abdominal pain, constipation, diarrhea, digestive tract disorders, dry mouth, flatulence, gastric pain, heart burn, hepatitis (rare), jaundice (rare), nausea, non-specific hepatic dysfunction (rare), vomiting, xerostomia
Musculoskeletal: Arthritis, general weakness, muscle cramps, musculoskeletal pain, polymyalgia-like syndrome, restless legs
Nervous: Confusion, decreased alertness, depression, dizziness, fullheadedness, hallucination, headache, impotence, increased dreaming, insomnia, lethargy, mental confusion, nervousness, nightmares, paresthesia, personality disorder, short-term memory loss, sleep disturbances, somnolence, tiredness, vertigo
Respiratory: Bronchospasm, dyspnea, rhinitis, shortness of breath, wheezing
Skin: Alopecia, hyperhidrosis, photosensitivity (very rare), pruritus, rash, worsening of psoriasis (very rare)
Special Senses: Blurred vision, dry eyes, eye irritation, hearing disorders (e.g., hypoacusis or deafness), tinnitus, visual disturbances
Others: Peyronie's disease, agranulocytosis, fatigue, increased or decreased antinuclear factor (ANF) levels, lassitude, retroperitoneal fibrosis, thrombocytopenia

Potential Undesirable Effects:
Cardiovascular: Intensification of AV block
Hematologic: Eosinophilia, nonthrombocytopenic purpura, thrombocytopenic purpura
Hypersensitivity Reactions: Erythematous rash, fever combined with aching and sore throat, laryngospasm, respiratory distress
Nervous: Reversible mental depression progressing to catatonia, acute reversible syndrome characterized by disorientation to time and place, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics

OVERDOSE AND TREATMENT
Metoprolol overdosage may be expected to produce effects that are mainly extensions of pharmacologic effects, including symptomatic bradycardia, severe hypotension, sinus bradycardia, AV block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting, and cyanosis.

The first manifestations of overdose occur within 20 minutes to 2 hours after metoprolol ingestion. The effects of massive overdose may persist for several days, despite decreasing plasma levels.

In cases of overdose, patients should be admitted to a hospital and should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood chemistry. Institute emergency supportive measures (e.g., artificial ventilation, cardiac pacing) if appropriate. Patients who have taken small overdose should be closely observed for manifestations of poisoning for at least 4 hours.

In acute metoprolol overdose, immediately empty the stomach by gastric lavage and/or activated charcoal. Initiate supportive and symptomatic treatment. For symptomatic bradycardia, IV atropine may be given; if bradycardia persists, IV isoproterenol hydrochloride may be administered cautiously. A vasopressor (e.g., dopamine, dobutamine, norepinephrine) may be given for severe hypertension; IV glucagon may be useful if hypotension is refractory to vasopressors. A beta-adrenergic agonist (e.g., isoproterenol) and/or a theophylline derivative may be given for bronchospasm. Monitor patients for evidence of cardiac arrhythmias during and after administration of the bronchodilator. Diazepam may be administered to control seizures. For heart failure, a cardiac glycoside, diuretic, and oxygen should be used; IV glucagons may also be useful.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

AVAILABILITY
Metoprolol tartrate (Cardiosel®) 50 mg Tablet, in blister pack x 20s (box of 100s)
Metoprolol tartrate (Cardiosel®) 100 mg Tablet, in blister pack x 20s (box of 100s)

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

DATE OF REVISION OF THE PACKAGE INSERT: May 2013

Reg. IPOPHIL

P30000012189

Manufactured by
AMHERST LABORATORIES, INC.
UNILAB Pharma Campus
Barangay Mamplasan, Biñan, Laguna, Philippines
Distributed by United Laboratories, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines
Under Authority by **UNILAB, INC.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Trusted Quality Healthcare