Metoprolol succinate Cardiosel®-OD

Rx

47.5 mg and 95 mg Extended-Release Tablets

BETA-ADRENOCEPTOR BLOCKER

FORMULATIONS

Each film-coated extended release tablet contains:

Metoprolol succinate ..... 47.5 mg
(Equivalent to Metoprolol tartrate 50 mg)

Each film-coated extended release tablet contains:

Metoprolol succinate..... 95 mg
(Equivalent to Metoprolol tartrate 100 mg)

PRODUCT DESCRIPTIONS

47.5 mg Extended-Release Tablet: White, circular, biconvex, film-coated tablet

95 mg Extended-Release Tablet: White, circular, biconvex, film-coated tablet

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Metoprolol is a beta-adrenergic receptor blocking agent which acts preferentially on $beta_1$ adrenoceptors, mainly located in cardiac muscle (cardioselective). 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, duration, and severity of both angina attacks and silent 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 decreases mortality in patients with suspected or confirmed myocardial infarction mainly due to a reduction in the risk of sudden death. This effect is presumed to partly be due to a dual mechanism, (1) a vagal effect with the blood-brain barrier beneficially influencing electrical stability of the heart, and (2) a sympathetic direct cardiac anti-ischemic effect beneficially influencing contractility, heart rate, and blood pressure. For both early and late intervention, decrease in mortality is also present in high risk patients with previous cardiovascular disease and in patients with diabetes mellitus.

Metoprolol decreases the risk for non-fatal myocardial infarction.

Metoprolol's anti-ischemic effects are shown in a reduction in chest pain during the acute infarction phase. Metoprolol decreases the incidence of recurrent myocardial infarction.

PHARMACOKINETICS

Metoprolol absorption is rapid and complete after oral administration. However, owing to extensive hepatic first-pass metabolism, about 50% of a single oral metoprolol dose reaches the systemic circulation. The extent of pre-systemic elimination differs between individuals because of genetic differences in oxidative metabolism. Although plasma profiles exhibit wide intersubject variability, they are reproducible within an individual. Upon repeated administration, the percentage of the dose systemically available is about 40% higher than after a single dose (about 70%). This may be due to partial saturation of the first-pass metabolism, or reduced clearance as a result of reduced hepatic blood flow. Ingestion of food may increase the systemic availability of a single oral dose by approximately 20% to 40%.

Metoprolol is rapidly distributed, with a volume of distribution of 3.2 to 5.6 L/kg. The half-life is not dose-dependent and does not change on repeated dosing. About 5 to 10% of metoprolol in plasma is protein-bound. Metoprolol crosses the placenta, and is found in breast milk. Metoprolol levels in cerebrospinal fluid are similar to those in plasma in patients with hypertension.

Metoprolol is extensively metabolized by enzymes of the cytochrome P450 system in the liver. Plasma concentration of the drug vary widely (up to 17-fold), perhaps because of genetically determined differences in the rate of metabolism. Metoprolol's oxidative metabolism is primarily via the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. About 7% of Caucasians and less than 1% Orientals are PMs. CYP2D6 PM exhibit several-fold higher plasma concentrations of metoprolol 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's average elimination half-life is 3 to 4 hours; it may be 7 to 9 hours in PM. About 95% of the dose can be recovered in the urine. Less than 5% of an oral dose is excreted unchanged in extensive metabolizers, while 30% in PM.

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
- Pediatric hypertension
- *Angina pectoris:* Long-term prophylaxis
- *Cardiac arrhythmias:* Disturbances of cardiac rhythm, including supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and ventricular extrasystoles
- *Myocardial infarction (MI):* Maintenance treatment after MI
- Functional heart disorders with palpitations
- Hyperthyroidism
- Prophylaxis of migraine headache

DOSAGE AND ADMINISTRATION

General Dosing Recommendations:
- Metoprolol extended-release tablet (metoprolol succinate) is to be taken once daily, preferably in the morning.
- The extended-release tablet should be swallowed whole with a glass of water. Do not chew or crush the extended-release tablet since this may cause inappropriate release and absorption of the drug.
- 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). Patients should not interrupt or discontinue metoprolol without consulting a physician.
- When switching from immediate release metoprolol tartrate to the extended-release metoprolol succinate, the same equivalent total daily dose of metoprolol should be used, since the metoprolol succinate dose is expressed in terms of metoprolol tartrate.
- Individualize dosage according to patient's clinical response.

INDICATION	RECOMMENDED ORAL METOPROLOL DOSE
Hypertension	**Adults** **Usual Initial Dose:** 50 mg daily given in a single dose, whether used alone or added to a diuretic. - Increase dose to 100 to 200 mg once daily or combined with other antihypertensive agents until optimum blood pressure reduction is achieved - Maximum effect in any given dosage level will be apparent after 1 week of treatment. **Children ≥ 6 years old (Who can swallow the extended-release tablet whole)** **Recommended Initial Dose:** 1 mg/kg once daily - Maximum initial dose should not exceed 50 mg once daily
Angina pectoris	**Usual Initial Dose:** 100 mg daily given in a single dose - Dosage may be increased at weekly intervals until optimum control of angina is obtained or there is pronounced slowing of heart rate. - Usual maintenance dosage: 100 to 400 mg once daily - Gradually reduce dosage over a period of 1 to 2 weeks if metoprolol is to be discontinued.
Cardiac arrhythmias	**Usual Dose:** 100 to 200 mg once daily
Myocardial infarction	**Treatment in the Acute Stage:** Begin with the intravenous (IV) administration of metoprolol. - ***In patients who tolerate the full IV dose (15 mg),*** administer metoprolol orally 15 minutes after the last IV dose at a dosage of **50 mg every 6 hours.** Thereafter, administer an oral maintenance dosage of **100 mg twice daily for a further 24 hours.** - ***In patients who appear not to tolerate the full IV dose,*** administer metoprolol with caution starting with a lower dose. **Maintenance Treatment:** Long-term oral metoprolol treatment in doses of 200 mg once daily has been shown to reduce the risk of death (including sudden death) and to reduce the risk of reinfarction (also in patients with diabetes mellitus).
Functional heart disorders with palpitation	**Recommended Dose:** 100 mg once daily - Dosage may be increased to 200 mg once daily if necessary
Hyperthyroidism	**Recommended Dose:** 100 to 200 mg once daily
Prophylaxis of migraine headache	**Recommended Dose:** 100 to 200 mg once daily
Or, as prescribed by a physician.	

Dosage in Renal Impairment: No dosage adjustment is needed

Dosage in Hepatic Impairment: Dosage adjustment is not normally needed in patients with liver cirrhosis since metoprolol has low protein binding. Dosage reduction should be considered when there are signs of serious hepatic impairment (e.g., shunt-operated patients)

CONTRAINDICATIONS

- Hypersensitivity to metoprolol or any other beta-blocker or any component of the product
- Severe bradycardia
- Grade 2 or 3 AV block and intranodal AV block
- Cardiogenic shock
- Decompensated cardiac failure (pulmonary edema, hypoperfusion or hypotension)
- Continuous or intermittent inotropic therapy acting through beta-receptor agonism
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Severe peripheral arterial circulatory disorder
- Acute myocardial infarction with the following conditions:
  - Heart rate < 45 beats/minute
  - P-Q interval ≥ 0.24 sec
  - Systolic blood pressure < 100 mmHg

WARNINGS AND PRECAUTIONS

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.

Pheochromocytoma: If metoprolol is used in the setting of pheochromocytoma, it 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.

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: Metoprolol should be used with caution in patients with diabetes mellitus if a beta-blocker is required. 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.

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.

Peripheral Vascular Disease: Use with caution in patients with peripheral vascular disease since beta-blockers may precipitate or aggravate symptoms of arterial insufficiency in these patients.

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 difficultly 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, monoamine oxidase (MAO) inhibitors]: 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 (e.g., diethyl ether): Some inhalation anesthetics may enhance the cardiopressant effect of beta-blockers.

Hepatic enzyme inducers/inhibitors: Enzyme inducing agents (e.g., rifampicin, phenytoin, phenobarbital) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g., cimetidine, hydralazine) 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 blood pressure lowering effect.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., indomethacin), other prostaglandin synthetase inhibitors: 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 (e.g., epinephrine): May provoke hypertensive reactions when used concomitantly with beta-blockers; however, this is less likely with therapeutic doses of $beta_1$-selective drugs than with non-selective beta-blockers.

Sympathetic ganglion blocking agents, other beta-blockers (i.e., eye drops): Patients given these drugs should be monitored closely.

Alcohol: Metoprolol may modify the pharmacokinetic parameters of alcohol.

Aluminum salts, cholestyramine, colestipol: May decrease beta-blocker absorption.

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.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY: Pregnancy Category C. Although there are no adequate and controlled studies to date in humans, metoprolol tartrate increased post-implantation loss and decreased neonatal survival in rats at doses up to 22 times (on a mg/m2 basis) the daily dose of 200 mg in a 60 kg patient. Since animal studies are not always predictive of human response, metoprolol should be used in pregnancy only if clearly needed.

LACTATION: Since metoprolol is excreted in breast milk, the drug should be used with caution in breastfeeding mothers.

GERIATRICS: Clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

CHILDREN: The safety and efficacy in children < 6 years old have not been established.

UNDESIRABLE EFFECTS

Cardiovascular: Arterial insufficiency (e.g., Raynaud's phenomenon), bradycardia, cold extremities, cardiogenic shock in patients with acute myocardial infarction, cerebrovascular disorder, chest pain, claudication, congestive heart failure, coronary artery disorder, deterioration of heart failure symptoms, edema, first-degree heart block, gangrene in patients with pre-existing severe peripheral circulatory disorders (very rare), hypotension, myocardial infarction, palpitations, peripheral edema, postural disorders (very rarely with syncope), precordial pain, second- or third-degree heart block, shortness of breath, syncope, ventricular tachycardia/ arrhythmia aggravated

Endocrine/Metabolic: Decreased libido, diabetes mellitus/diabetes mellitus aggravated, hyperglycemia, hypoglycemia, weight gain, changes in blood concentrations of triglycerides and cholesterol; ***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 (very rare), hiccups, jaundice, liver function test abnormalities, nausea, non-specific hepatic dysfunction, vomiting, xerostomia

Hematologic: Agranulocytosis, eosinophilia, nonthrombocytopenic and thrombocytopenic purpura

Musculoskeletal: Arthralgia, arthritis, general weakness, muscle cramps, musculoskeletal pain, polymyalgia-like syndrome, restless legs

Nervous: Amnesia, anxiety, confusion, depression, dizziness, fullheadedness, hallucination, headache, impotence/sexual dysfunction, impaired concentration, increased dreaming, insomnia, lethargy, mental confusion, memory impairment, nervousness, nightmares, paresthesia, short-term memory loss, sleep disturbances, somnolence, tiredness, vertigo

Respiratory: Bronchospasm, dyspnea/dyspnea on exertion, pneumonia, rhinitis, wheezing

Skin: Alopecia, hyperhidrosis, photosensitivity (very rare), pruritus, rash (in the form of urticaria psoriasiform and dystrophic skin lesions), urticaria, psoriasis aggravated (very rare)

Special Senses: Blurred vision, conjunctivitis, dry eyes, eye irritation, taste disturbances, tinnitus, visual disturbances

Others: Peyronie's disease, accident and/or injury, fatigue, increased or decreased antinuclear factor (ANF) levels, retroperitoneal fibrosis

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 neuropyschometrics

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.

In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible, the patient should be treated under intensive care conditions.

On the basis of metoprolol's pharmacologic actions, the following general measures should be employed:

Elimination of Metoprolol: Perform gastric lavage

Bradycardia: Administer atropine. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: Administer vasopressor (e.g., dopamine, norepinephrine)

Bronchospasm: Administer $beta_2$-stimulating agent and/or theophylline derivative

Cardiac failure: Administer digitalis glycoside and diuretics. In shock resulting from inadequate cardiac contractility, consider administration of dobutamine, isoproterenol, or glucagons.

STORAGE CONDITION

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

AVAILABILITY:

Metoprolol succinate (Cardiosel®-OD) 47.5 mg Extended-Release Tablet
Blister pack of 10's (Box of 100's).

Metoprolol succinate (Cardiosel®-OD) 95 mg Extended-Release Tablet
Blister pack of 10's (Box of 100's).

CAUTION

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

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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Plot No. B-4/5/6, M.I.D.C., Paithan, Aurangabad, 431148 Maharashtra State, India
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