For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

METOCARD XL 50

(Metoprolol Succinate Extended Release Tablets)

METOCARD XL 50

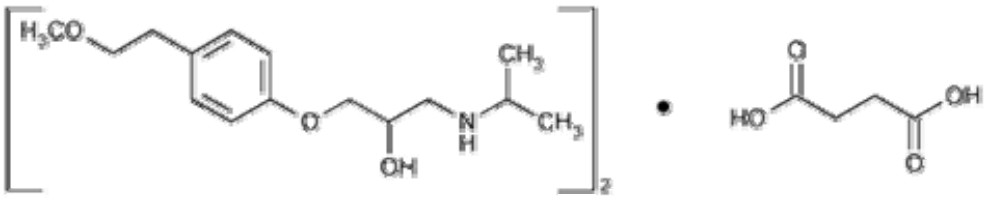
Each film coated extended release tablet contains:
Metoprolol Succinate U.S.P
Equivalent to Metoprolol Tartrate 50 mg
Colour: Lake of Quinoline Yellow and Titanium Dioxide

WARNING: ISCHEMIC HEART DISEASE:

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol Succinate Extended Release tablet, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Metoprolol Succinate Extended Release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Metoprolol Succinate Extended Release tablet therapy abruptly even in patients treated only for hypertension.

DESCRIPTION

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration.
Chemical Name: Its chemical name is (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt).
Molecular Weight: 652.81
Molecular Formula: $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$
Structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic

outflow to the periphery; and (3) suppression of renin activity.

Pharmacodynamic
Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Metoprolol is a β_1-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits β_2 adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The relative β_1-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the β_2-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent β_1-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an Emax model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta1-blockade. Beta1-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative beta1-selectivity of metoprolol diminishes and blockade of beta2-adrenoceptors increases at plasma concentration above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta2-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Pharmacokinetics
Adults
In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.
Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally,

it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.
Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardio selectivity.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Metoprolol Succinate Extended Release Tablets are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of Metoprolol Succinate Extended Release Tablets average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Metoprolol Succinate Extended Release Tablets, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, β_1-blockade is comparable and dose-related. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol Succinate Extended Release Tablets administration.

Pediatrics
The pharmacokinetic profile of Metoprolol Succinate Extended Release Tablets was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol was similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.
Metoprolol pharmacokinetics has not been investigated in patients < 6 years of age.

INDICATIONS AND USAGE
For the treatment of essential hypertension in adults

CONTRAINDICATIONS
Metoprolol Succinate Extended Release tablet is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

SPECIAL WARNINGS
Ischemic Heart Disease
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of

angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Metoprolol Succinate Extended Release Tablet, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1- 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Metoprolol Succinate Extended Release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. 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 may be prudent not to discontinue Metoprolol Succinate Extended Release tablet therapy abruptly even in patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol Succinate Extended Release Tablet. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol Succinate Extended Release Tablet. It may be necessary to lower the dose of Metoprolol Succinate Extended Release Tablet or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol Succinate Extended Release Tablet.

Bronchospastic diseases

Patients with bronchospastic diseases should, in general, not receive β blockers. Because of its relative β_1 selectivity, however, Metoprolol Succinate Extended Release tablet may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because β_1 selectivity is not absolute, use lowest possible dose of Metoprolol Succinate Extended Release tablet. Bronchodilators, including a β_2 agonist should be administered concomitantly,

Pheochromocytoma

If Metoprolol Succinate Extended Release tablet is used in the setting of pheochromocytoma, it should 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

Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death.

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and hypoglycemia

Beta blockers may mask tachycardia occurring with hypoglycemia but other manifestations such as dizziness and sweating may not be significantly affected.

Hepatic Impairment

Consider initiating Metoprolol Succinate Extended Release tablet therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy,

while monitoring closely for adverse events.

Thyrotoxicosis
Beta-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

Anaphylactic Reaction
While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease
Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Calcium Channel Blockers
Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

DRUG INTERACTIONS
Catecholamine Depleting Drugs:
Catecholamine-depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with Metoprolol Succinate Extended Release tablet plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
CYP2D6 Inhibitors:

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two-to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardio selectivity of metoprolol.
Digitalis, Clonidine, and Calcium Channel Blockers:

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

SPECIAL POPULATIONS

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on an mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Consider possible infant exposure when Metoprolol Succinate Extended Release tablet is administered to a nursing woman.

Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of Metoprolol Succinate Extended Release tablet (0.2, 1.0 or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary end point (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

- Dose-response for reduction in DBP,
- 1.0 mg/kg vs. placebo for change in SBP, and
- 2.0 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerable greater reductions were seen in some individuals. No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients. Safety and effectiveness of Metoprolol Succinate Extended Release tablet have not been established in patients < 6 years of age.

Geriatric Use

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No studies have been reported with Metoprolol Succinate Extended Release tablet in patients with hepatic impairment. Because Metoprolol Succinate Extended Release tablet is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

Renal Impairment

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are reported under widely varying conditions, adverse reaction rates reported in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for immediate release metoprolol tartrate. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.

Heart Failure

In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing Metoprolol Succinate Extended Release tablet in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of Metoprolol Succinate Extended Release tablet receiving patients discontinued for adverse events vs. 12.2% of placebo patients.

The table below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the Metoprolol Succinate Extended Release tablet receiving group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Reactions Occurring in the MERIT-HF Study at an Incidence ≥ 1 % in the Metoprolol Succinate Extended Release tablet Group and Greater Than Placebo by More Than 0.5 %

	Metoprolol Succinate Extended Release tablet receiving group (N=1990) % of patients	Placebo (N=2001) % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Post-operative Adverse Events: In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta–blocker therapy, Metoprolol Succinate Extended Release tablet 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. Metoprolol Succinate Extended Release tablet use was associated with a higher incidence of bradycardia, hypotension, stroke and death compared to placebo.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Metoprolol Succinate Extended Release tablet. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea.

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.
Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.
Hypersensitive Reactions: Pruritus.
Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance

Potential Adverse Reactions
In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol Succinate Extended Release tablet.
Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block.
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: laryngospasm, and respiratory distress.

Laboratory Test findings
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

OVERDOSAGE
Signs and Symptoms: Overdosage of Metoprolol Succinate Extended Release tablet may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment: Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Bronchospasm: Administer a beta2-agonist, including albuterol inhalation, or an oral theophylline derivative.

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.

DOSAGE AND ADMINISTRATION
Metoprolol Succinate Extended Release tablet is intended for once daily administration. For treatment of hypertension and angina, when switching from immediate release metoprolol to Metoprolol Succinate Extended Release tablet, the same total daily dose of Metoprolol Succinate Extended Release tablet should be used. Dosages of Metoprolol Succinate Extended Release tablet should be individualized and titration may be needed in some patients.

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

Pediatric Hypertensive Patients ≥ 6 Years of age: A pediatric clinical hypertension study in patients 6 to 16 years of age did not meet its primary endpoint (dose response for reduction in SBP), however some other endpoints demonstrated effectiveness. If selected for treatment, the recommended starting dose of Metoprolol Succinate Extended Release tablet is 1.0 mg/kg once daily however, the maximum initial dose should not exceed 50 mg once daily. The minimum available dose is 12.5 mg Metoprolol Succinate Extended Release tablet. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients. Metoprolol Succinate Extended Release tablet is not recommended in pediatric patients < 6 years of age.

EXPIRY DATE
Don not use letter than the date of expiry.

STORAGE
Store in a dry place below 30 ^{o}C, Protected from light

PRESENTATION
Metocard XL 50 is available in strip pack of 10 tablets

MARKETED BY:
torrent

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