

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

METOCARD XL 100
(Metoprolol Succinate Extended Release Tablets)

COMPOSITION

METOCARD XL 100

Each film coated extended release tablet contains:

Metoprolol succinate I.P.

Equivalent to Metoprolol Tartrate.....100mg

Colour: Lake of Quinoline Yellow and Titanium Dioxide

WARNING: ISCHEMIC HEART DISEASE

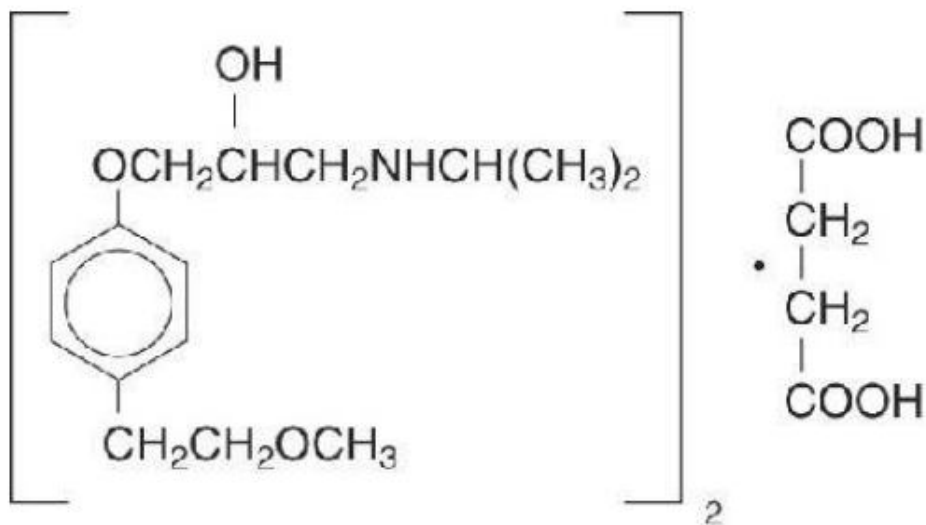
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol succinate, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1-2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate metoprolol succinate, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol succinate in patients treated only for hypertension.

DESCRIPTION

Metoprolol succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. Metoprolol succinate has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 and 190 mg of metoprolol succinate equivalent to 25,

50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±) 1(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt).

Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, paraffin.

CLINICAL PHARMACOLOGY

Pharmacodynamic:

Mechanism of Action

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.

Heart Failure: The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.

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 beta₁-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta₂-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 beta₁-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta₂-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 FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-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 30-540nmol/L. The relative beta₁-selectivity of metoprolol diminishes and blockade of beta₂-adrenoreceptors increases at plasma concentration above 300nmol/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. In other studies, treatment with metoprolol succinate produced an improvement in left ventricular ejection fraction. metoprolol succinate was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

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 metoprolol succinate 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. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of metoprolol succinate 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 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, 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 [see Clinical Pharmacology (12)]. 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 administration.

Pediatrics: The pharmacokinetic profile of metoprolol succinate 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 were 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 have not been investigated in patients < 6 years of age

Non clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more

frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

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

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, the same total daily dose of Metoprolol Succinate Extended Release tablet should be used. Individualize the dosage of metoprolol succinate. Titration may be needed in some patients.

Metoprolol Succinate tablets are scored and can be divided; however, do not crush or chew the whole or half tablet.

Hypertension

Adult: - The usual initial dosage is 25 to 100mg 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 400mg per day have not been studied.

Paediatric Hypertensive patients \geq 6 Years of age. A paediatric hypertension study in patients 6 to 16 years of age did not meet its primary end point (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 1.0mg/kg once daily. However, the maximum initial dose should not exceed 50mg once daily. The minimum available dose is 12.5mg Metoprolol Succinate Extended Release tablet. Dosage should be adjusted according to blood pressure response. Doses above 2.0mg/kg (or in excess of 200mg) once daily have not been studied in paediatric patients. Metoprolol Succinate Extended Release tablet is not recommended in paediatric patients < 6 years of age.

INDICATIONS

For the treatment of essential hypertension in adults.

CONTRAINDICATIONS

Metoprolol Succinate 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.

WARNING AND PRECAUTION

Heart Failure

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

Bronchospastic Disease

Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta1 cardio-selectivity, however, Metoprolol Succinate may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of Metoprolol Succinate. Bronchodilators, including beta2-agonists, should be readily available or administered concomitantly.

Pheochromocytoma

If Metoprolol Succinate 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 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 of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may 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. Observe patients treated with Metoprolol Succinate plus a catecholamine depletor 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 cardioselectivity of metoprolol.

Digitalis, Clonidine, and Calcium Channel Blockers-

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are co-administered, 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

ADVERSE REACTIONS

The following adverse reactions are described elsewhere in labeling:

1. Worsening angina or myocardial infarction.
2. Worsening heart failure
3. Worsening AV block.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed 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 reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.

Heart Failure: In the MERIT-HF study comparing Metoprolol Succinate in daily doses up to 200 mg (mean dose 159 mg once-daily; n=1990) to placebo (n=2001), 10.3% of Metoprolol Succinate patients discontinued for adverse reactions vs. 12.2% of placebo patients.

The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of $\geq 1\%$ in the Metoprolol Succinate group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

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 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. Metoprolol Succinate use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1.0% vs. 0.5%; HR 2.17; 95% CI 1.26, 3.74) and death (3.1% vs. 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use or immediate-release metoprolol. 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 adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol Succinate.

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, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress

OVERDOSAGE

Signs and Symptoms - Overdosage of Metoprolol Succinate 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

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 a mg/m² 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, use this drug 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 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 (0.2, 1.0 or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary

endpoint (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 considerably 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 have not been established in patients < 6 years of age.

Geriatric Use

Clinical studies of Metoprolol Succinate in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger

Hepatic Impairment

No studies have been performed with Metoprolol Succinate in patients with hepatic impairment. Because Metoprolol Succinate 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.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a dry place below 30° C, Protected from light.

PRESENTATION

Metocard XL 100 is available in strip pack of 10 tablets.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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IN/Metocard XL 100mg/Mar 2016/01/PI