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

METOCARD XL 75

1. Generic Name

Metoprolol Succinate Prolonged-Release Tablets.

2. Qualitative and quantitative composition

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P. 71.25 mg

Equivalent to Metoprolol Tartrate 75 mg

Colours: Lake of Quinoline Yellow and Titanium dioxide I.P.

The excipients used are carbomer Homopolymer, microcrystalline cellulose, HPMC, colloidal silicon dioxide (Aerosil), magnesium stearate, hydroxy propyl methyl cellulose, Poly ethylene glycol, Titanium dioxide, Lake of Quinoline yellow.

3. Dosage form and strength

Dosage: Film coated prolonged-release tablet

Strength: 75 mg.

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of essential hypertension in adults only.

4.2 Posology and method of administration

Posology

The following dosage regimes are intended only as a guideline and should always be adjusted to the individual requirements of the patient but should not exceed 400 mg/day.

Dose: As directed by the Physician.

Metoprolol may be administered with benefit both to previously untreated patients with hypertension and to those in whom the response to previous therapy is inadequate. In the latter type of patient, the previous therapy may be continued and metoprolol added in to the regime with adjustment of the previous therapy if necessary.

Hepatic impairment

In patients with significant hepatic dysfunction dosage reduction may be advised.

Renal impairment

Dose adjustment is not warranted in renal impairment.

Method of Administration

For oral administration.

4.3 Contraindications

Known hypersensitivity to metoprolol, related derivatives, and any other β-blockers or to any of the excipients listed in section 6.1.

- Second-or third-degree atrioventricular block
- Uncontrolled heart failure
- Clinically relevant sinus bradycardia (< 45-50 bpm)
- Sick sinus syndrome (unless a pacemaker is in situ).
- Prinzmetal's angina
- Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock
- Severe peripheral arterial disease
- Asthma and history of bronchospasm
- Untreated phaeochromocytoma
- Metabolic acidosis
- Concomitant intravenous administration of calcium blockers of the type verapamil or diltiazem or other antiarrhythmic (such as disopyramide) is contraindicated (exception: intensive care unit).
- Hypotension
- Diabetes if associated with frequent episodes of hypoglycaemia
- Chronic obstructive pulmonary disease

4.4 Special warnings and precautions for use

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardio selective beta blockers may have less effect on lung function than non-selective beta blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Therapy with a $beta_2$-stimulant may become necessary or current therapy require adjustment. Therefore, non-selective beta blockers should not be used for these patients, and $beta_1$-selective blockers only with the utmost care.

Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta blocker should be gradual.

Metoprolol Tartrate tablets may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.

When a beta blocker is being taken, a serious, sometimes even life-threatening deterioration in cardiac function can occur, in particular in patients in whom the action of the heart is dependent on the presence of sympathetic system support. This is due less to an excessive beta-blocking effect and more to the fact that patients with marginal heart function tolerate poorly a reduction in sympathetic nervous system activity, even where this reduction is slight. This causes contractility to become weaker and the heart rate to reduce and slows down AV conduction. The consequence of this can be pulmonary oedema, AV block, and shock. Occasionally, an amlodipine Besylate g AV conduction disturbance can deteriorate, which can lead to AV block. In patients with a phaeochromocytoma, an alpha blocker should be given concomitantly.

Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, Metoprolol should be administered with caution to patients having, or suspected of developing, thyrotoxicosis, and both thyroid and cardiac function should be monitored closely

Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to increase in blood pressure and bradycardia.

Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged release tablets than when using regular tablet forms for $beta_1$ selective beta blockers and significantly lower than when using nonselective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy.

In case of unstable or insulin dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.

Patients with anamnestic ally known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.

Beta blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may unmask myasthenia gravis.

In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose mal-absorption should not take this medicine.

Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

4.5 Drugs interactions

Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichloroethylene, are best avoided. In a patient under beta-blockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.

- It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypo-glycaemia (tachycardia).

- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculoventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.

Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers.

- Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

- Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-blockers used in conjunction with clonidine increase the risk of "rebound hypertension". If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

- The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.

- NSAIDs (especially indomethacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

- Digitalis Glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase in auriculo-ventricular conduction time.

- The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.

- The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.

- Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

- Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolized beta blockers.

- As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.

- Class 1 antiarrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrialconduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.

- During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.

- Metoprolol may impair the elimination of lidocaine.

- Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers.

- Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen induced fluid retention may lead to increased blood pressure.

- Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects.

- Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking.

- Concurrent use requires careful monitoring.

- Concurrent use of aldesleukin may result in an enhanced hypotensive effect.

- Concurrent use of alprostadil may result in an enhanced hypotensive effect.

- There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.

- Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.

- Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.

- The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

It is recommended that metoprolol should not be administered during pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant. Should therapy with metoprolol be employed, special attention should be paid to the foetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate.

Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks' gestation. Although the drug crosses the placental barrier and is present in cord blood no evidence of foetal abnormalities has been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long time treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause bradycardia in the foetus and the new-born child, there are also reports of hypoglycaemia and hypotension in newborn children.

Animal experiments have shown neither teratogenic potential nor other adverse events on the embryo and/or foetus relevant to the safety assessment of the product. Treatment with metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours post-partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Lactation

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. The risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity). Cases of neonatal hypoglycaemia and bradycardia have been described with beta-blockers with low plasma protein binding. Metoprolol is excreted in human milk. Even though the metoprolol concentration in milk is very low, breast-feeding should be discontinued during treatment with metoprolol. In case of treatment during breast feeding, infants should be monitored carefully for symptoms of beta blockade.

4.7 Effects on ability to drive and use machines

As with all beta-blockers, metoprolol can affect patient's ability to drive and operate machinery. It should be taken into account that occasionally dizziness and fatigue may occur. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Frequency estimates: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Thrombocytopenia, agranulocytosis	
Psychiatric disorders				Depression, nightmares, Nervousness, anxiety, impotence	Hallucinations, personality disorder, Amnesia / memory impairment	
Nervous system disorders		Dizziness, headache		Alertness decreased, somnolence or insomnia, paraesthesia		
Eye disorders					Visual disturbance (e.g. blurred vision, dry eyes and/or eye irritation	
Ear and labyrinth disorders					Tinnitus, and, in doses exceeding those recommended, "hearing disorders (eg. Hypoacusis or deafness)	
Cardiac disorders		Bradycardia		Heart failure, cardiac arrhythmias, palpitation	Cardiac conduction disorders, precordial pain	Increase in exAmlodipineg Besylateg intermittent claudication

Vascular disorders		Orthostatic hypotension (occasionally with syncope)		Oedema, Raynaud's phenomenon	Gangrene in patients with pre-ex Amlodipineg Besylate g severe peripheral circulatory disorders	
Respiratory, thoracic and mediastinal disorders		Exertional dyspnoea		Bronchospasm(which may occur in patients without a history of obstructive lung disease)	Rhinitis	
Gastrointestinal disorders		Nausea and vomiting, abdominal pain		Diarrhoea or constipation	Dry mouth	Retroperitoneal fibrosis *
Hepatobiliary disorders						Hepatitis
Skin and subcutaneous tissue disorders				Skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions) s	Photosensitivity, hyperhidrosis, alopecia, worsening of psoriasis	Occurrence of antinuclear antibodies (not associated with SLE)
Musculoskeletal and connective tissue disorders				Muscle cramps	Arthritis	
Reproductive system and breast disorders					Disturbances of Libido and potency	Peyronie's disease *

General disorders and administration site conditions		Fatigue			Dysgeusia (Taste disturbances)	
Investigations					Weight increase, liver function test abnormal	

* (relationship to Metoprolol has not been definitely established).

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

- **Reporting of suspected adverse reactions**

  Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia. The first manifestations usually appear 20 minutes to two hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive- care ward. Absorption of any drug material still present in the gastrointestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required.

Bradycardia or extensive vagal reactions should be treated by administering atropine or methyl atropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v.

infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or Haemoperfusion may be considered

5. Pharmacological properties

5.1 Mechanism of Action

Metoprolol is a beta-1 selective beta blocker.

It has a relatively greater blocking effect on beta receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of the fatty acids from fat stores) than on beta receptors which are chiefly involved in Broncho and vasodilation.

5.2 Pharmacodynamics properties

Pharmacotherapeutic group: Beta blockers, selective.

ATC code: C 07 AB 02.

Mechanism of action

Metoprolol is a beta-1 selective beta blocker.

It has a relatively greater blocking effect on beta receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of the fatty acids from fat stores) than on beta receptors which are chiefly involved in Broncho and vasodilation.

Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect.

Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart. Metoprolol reduces tachycardia, decreases the cardiac output and the contractility, and lowers the blood pressure.

If required, metoprolol may be administered concomitantly with a beta-2 agonist to patients with symptoms of obstructive pulmonary disease.

5.3 Pharmacokinetic properties

Absorption

Metoprolol is readily and completely absorbed from the gastrointestinal tract. Metoprolol is absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.

Distribution

Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ml. Metoprolol is widely distributed, it crosses the blood brain barrier, the placenta. It is slightly bound to plasma protein. The medicinal product is approx. 5–10% bound to plasma proteins.

Biotransformation

Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute. It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination

The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk.

Special population

Elderly:

In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients shows no significant differences.

Renal impairment:

Renal dysfunction has barely any effect on the bioavailability of metoprolol. However, the excretion of metabolites is reduced. In patients with a glomerular filtration rate of less than 5 ml/minute, a significant accumulation of metabolites has been observed. This accumulation of metabolites, however, produces no increase in the beta blockade.

Hepatic impairment:

The pharmacokinetics of metoprolol are influenced only minimally by reduced hepatic function. However, in patients with serious hepatic cirrhosis and a portacaval shunt, the bioavailability of metoprolol can increase, and the total clearance can be reduced. Patients with portacaval anastomosis had a total clearance of approx. 0.3 litres/minute and AUC values that were 6 times higher than those found in healthy persons.

Severe angina pectoris

Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensive is influenced by this characteristic. In exceptional cases, however, very high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment

It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of preex Amlodipine Besylate g bronchospastic complaints.

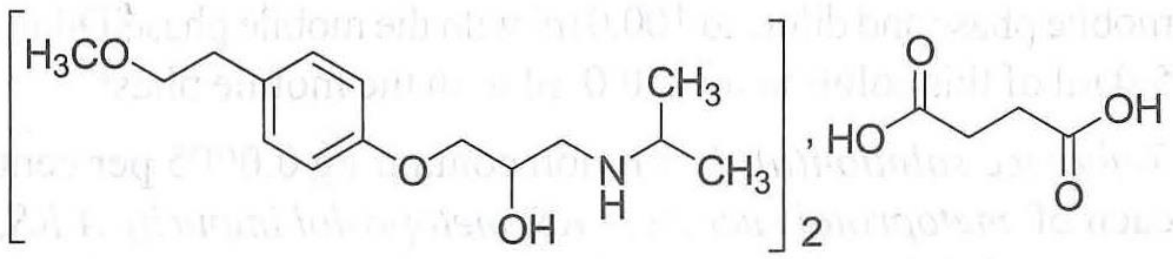
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

There are no preclinical data of relevance to the prescriber.

7. Description

Metoprolol Succinate is (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl)phenoxy]propan-2- ol succinate. Having molecular formula (C15H25NO3)2, C4H6O4 and molecular weight 652.8. The chemical structure is:



Yellow coloured round bicovex film coated tablets plain on both the sides. The excipients used are carbomer homopolymer, microcrystalline cellulose, HPMC, colloidal silicon dioxide (aerosil), magnesium stearate, hydroxy propyl methyl cellulose, Poly ethylene glycol, Titanium dioxide, lake of quinoline yellow.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

METOCARD XL 75 **is packed in blister strips of 10 tablets.**

8.4 Storage and handing instructions

Store at a temperature not exceeding 30^0c, protected from light and moisture.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.6 Contents of the pack and other information

9.1.What METOCARD XL 75 are and what they are used for.

Metoprolol tartrate contains metoprolol tartrate, which belongs to a group of medicines called beta-blockers. Metoprolol tartrate reduces the effect of the stress hormones on the heart in connection with physical and mental exertion. This results in the heart beating slower (pulse rate is reduced).

METOCARD XL 75 is used for the treatment of essential hypertension in adults only.

9.2 What you need to know before you take METOCARD XL 75

Do not take Metoprolol Tartrate tablets if you:

- are allergic to metoprolol, other beta-blockers or any other ingredients of this medicine
- suffer with heart conduction or rhythm problems
- have severe or uncontrolled heart failure
- are in shock caused by heart problems
- suffer with blocked blood vessels, including blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue)
- have a slow heart rate or have suffered a heart attack which has been complicated by a significantly slow heart rate
- suffer from a tight, painful feeling in the chest in periods of rest (Prinzmetal's angina)
- have or have had breathing difficulties or asthma including COPD (Chronic Obstructive Pulmonary Disease causing cough, wheezing or breathlessness, phlegm or increase in chest infections)
- suffer with untreated phaeochromocytoma (high blood pressure due to a tumour near the kidney)
- suffer from increased acidity of the blood (metabolic acidosis)
- have low blood pressure
- suffer with diabetes associated with frequent episodes of low blood sugar (hypoglycaemia)
- have liver or kidney disease or failure
- Are given other medicines for blood pressure by injection especially verapamil, diltiazem or disopyramide.

Warnings and precautions

- Talk to your doctor or pharmacist before using Metoprolol Tartrate 50 mg tablets if you:
- have a history of allergic reactions, for example to insect stings, foods or other substances,
- have diabetes mellitus (low blood sugar levels may be hidden by this medicine)
- have controlled heart failure.
- have a slow heart rate or blood vessel disorder. suffer from treated phaeochromocytoma (high blood pressure due to tumour near the kidney)
- have or have suffered from psoriasis (severe skin rashes)
- have liver cirrhosis
- are elderly
- have myasthenia gravis.
- If you suffer from dry eyes Anaesthetics and surgery

  If you are going to have an operation or an anaesthetic, please tell your doctor or dentist that you are taking Metoprolol Tartrate tablets, as your heart beat might slow down too much.

Taking other medicines

Do not take Metoprolol Tartrate tablets if you are already taking:

- monoamine oxidase inhibitors (MAOIs) for depression
- other blood pressure lowering medicines such as verapamil, nifedipine and diltiazem
- disopyramide or quinidine (to treat irregular heartbeat (arrhythmia)

Children

Do not give this medicine to children.

Other medicine and Metoprolol Tartrate tablets

Tell your doctor or pharmacist if you are taking, have taken recently or might take any other medicines.

- medicines used to treat stomach ulcers such as cimetidine
- medicines used to treat high blood pressure such as hydralazine, clonidine or prazosin
- medicines used to treat irregular heart rhythm such as amiodarone and propafenone
- medicines used to treat depression such as tricyclic or SSRI antidepressants
- medicines used to treat epilepsy such as barbiturates
- medicines used to treat mental illness such as phenothiazines
- anaesthetics such as cyclopropane or trichloroethylene
- medicines used to treat some cancers, particularly cancer of the kidney such as aldesleukin
- medicines used to treat erectile dysfunction such as alprostadil
- anxiolytics or hypnotics (e.g. temazepam, nitrazepam, diazepam)
- indometacin or celecoxib (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs))
- rifampicin (antibiotic) or terbinafine (antifungal)
- oestrogens such as a contraceptive pill or hormone replacement therapy
- corticosteroids (e.g. hydrocortisone, prednisolone)
- Other beta-blockers e.g. eye drops.
- adrenaline (epinephrine) or noradrenaline (norepinephrine), used in anaphylactic shock or other sympathomimetic
- medicines used to treat diabetes
- lidocaine (a local anaesthetic)
- moxisylyte (used in Raynaud's syndrome)
- medicines used to treat malaria such as mefloquine
- medicines used to prevent nausea and vomiting such as tropisetron
- medicines used to treat asthma such as xanthines such as aminophylline or theophylline
- medicines to treat migraines such as ergotamine
- medicines used to treat heart conditions such as cardiac glycosides e.g. digoxin
- medicines used to treat rheumatoid arthritis such as hydroxychloroquine
- Diphenhydramine (sedative antihistamine).

Metoprolol Tartrate tablets and alcohol

You are advised to avoid alcohol whilst taking this medicine. Alcohol may increase the blood pressure lowering effect of Metoprolol Tartrate tablets.

Pregnancy and breast-feeding

Metoprolol Tartrate tablets are not recommended during pregnancy or breast-feeding. If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Driving and using machines Metoprolol Tartrate tablets may make you feel tired and dizzy. If affected, patients should not drive or operate machinery.

9.3 How to use METOCARD XL 75

Always take Metoprolol Tartrate tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If you take more Metoprolol Tartrate tablets than you should

If you have accidentally taken more than the prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist at once.

Symptoms of overdose are

low blood pressure (fatigue and dizziness), slow pulse, heart conduction problems, shortness of breath, unconsciousness, coma, , cardiac arrest, feeling and being sick ,blue colouring of the skin, low blood sugar levels and high levels of potassium in the blood.

If you forget to take Metoprolol Tartrate tablets

If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Then go on as before.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Metoprolol Tartrate tablets

Do not suddenly stop taking Metoprolol Tartrate tablets as this may cause worsening of heart failure and increase the risk of heart attack. Only change the dose or stop the treatment in consultation with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or **pharmacist.**

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Stop treatment and contact a doctor at once if you have the following symptoms of an allergic reaction such as itching, difficulty breathing or swelling of the face, lips, throat or tongue.

Tell your doctor if you notice any of the following side effects or notice any other effects not listed:

Common (may affect up to 1 in 10 people):

- tiredness
- dizziness
- headache
- a slow heart rate
- feeling faint on standing due to low blood pressure
- shortness of breath with or without strenuous physical activity
- feeling or being sick
- stomach pain

Rare (may affect up to 1 in 1,000 people):

- depression
- nightmares
- nervousness
- anxiety
- sexual dysfunction or reduced sex drive
- inability to think clearly
- sleepiness or difficulty in sleeping
- tingling or 'pins and needles'
- difficulty breathing
- heart failure
- irregular heart rate
- palpitation
- water retention causing swelling
- Raynaud's phenomenon (causing pain, numbness, coldness and blueness of the fingers)
- diarrhoea or constipation
- skin rash
- muscle cramps
- **Very rare (may affect up to 1 in 10,000 people):**
- changes in the results of blood tests
- effects on blood clotting causing easy or unexplained bruising
- changes in personality
- confusion
- hallucinations
- visual disturbances
- dry or irritated eyes
- ringing in the ears
- loss of hearing with high doses
- heart conduction problems
- chest pain
- gangrene in patients with severe poor circulation
- runny nose
- dry mouth
- weight gain sensitivity to light
- increased sweating
- hair loss
- worsening or new psoriasis
- joint inflammation (arthritis)
- disturbances of sexual desire and performance
- changes in liver function tests
- taste disorders

  Not known (frequency cannot be estimated from the available data):
- worsening or development of limping
- hepatitis (symptoms include fever, sickness and yellowing of the skin or whites of the eyes)
- Peyronie's syndrome (bending of the penis)
- symptoms of high levels of the thyroid hormone or low blood sugar may be hidden
- increase in blood fats or decrease in cholesterol

- retroperitoneal fibrosis (symptoms include lower back pain, high blood pressure)
- Occurrence of antinuclear antibodies not associated with systemic lupus erythematosus (SLE).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store METOCARD XL 75

Store at a temperature not exceeding 30^0c, protected from light and moisture

9.6 Contents of the pack and other information

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P. 71.25 mg

Equivalent to Metoprolol Tartrate 75 mg

Colours: Lake of Quinoline Yellow and Titanium dioxide I.P.

The excipients used are carbomer homopolymer, microcrystalline cellulose, HPMC, colloidal silicon dioxide (aerosil), magnesium stearate, hydroxy propyl methyl cellulose, Poly ethylene glycol, Titanium dioxide, lake of quinoline yellow.

10. Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135.

11.Details of permission or licence number with date

M/563/2010 issued on 5.04.2017

12.Date of revision

October 2019

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ METOCARD XL 75 mg/OCT-19/02/PI