GenRx METOPROLOL TABLETS

NAME OF THE MEDICINE
Metoprolol tartrate.

Chemical Name: di([RS]-3-[4-(2-methoxyethyl)phenoxy]-1-(isopropylamino)propan-2-ol] tartrate.

Structural Formula:

- Molecular Formula: \((C_{15}H_{25}NO_3)_2\cdot C_4H_6O_6\)
- Molecular Weight: 684.82
- CAS Registry Number: 56392-17-7
- Melting Point: approximately 120°C.

DESCRIPTION
Metoprolol tartrate is a white crystalline powder. The powder is practically odourless. It is very soluble in water, soluble in chloroform, methylene chloride and alcohol, and almost insoluble in benzene, diethylether and acetone.

PHARMACOLOGY
Pharmacokinetics
Absorption and Distribution
Metoprolol is rapidly and almost completely (more than 95%) absorbed from the gastrointestinal tract. It is rapidly and extensively distributed to the extravascular tissues. The volume of distribution is 5.6 L/kg. At therapeutic concentrations, approximately 12% is bound to human serum proteins.

Metabolism and Elimination
Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolisers phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolisers. CYP2D6 poor metabolisers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolisers with normal CYP2D6 activity. Although the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug,
caution should be exercised when administering metoprolol to poor metabolisers.

Studies with the radioactively labelled drug have shown that more than 90% of the dose is excreted in the urine within 72 hours, mainly in the form of known metabolites. Only about 3% of the administered dose is excreted unchanged in the urine in 72 hours. The rate of renal excretion of metoprolol has a linear relationship to its plasma concentration. Metoprolol is excreted mainly by glomerular filtration.

Long-term studies have shown that metoprolol neither enhances nor inhibits its own metabolism.

The elimination half-life of metoprolol tartrate is between three and five hours.

**Dose-Response**

The duration of the β-blocking effect is dose dependent (as measured by reduction of exercise heart rate).

**Pharmacokinetics in the Elderly**

Elderly subjects showed no significant differences in the plasma concentrations of metoprolol as compared with young subjects, in a study involving eight healthy elderly (mean age 74.5 years) and eight healthy young (mean age 26.3 years) subjects.

**Pharmacodynamics**

Metoprolol is structurally related to other cardioselective β-blockers. It is a relatively cardioselective β-adrenoceptor blocking drug without intrinsic sympathomimetic activity, and is suited for the treatment of hypertension. It acts on β1-receptors mainly located in the heart at lower doses than those needed to influence the β2-receptors mainly located in the bronchi and peripheral vessels. It reduces blood pressure in patients with hypertension, in both the standing and supine position. It also reduces the extent of rises in blood pressure occurring in response to physical and mental stress.

In angina pectoris metoprolol reduces the frequency and severity of the attacks and the need for glyceryl trinitrate relief, and increases exercise tolerance.

Metoprolol has been shown to reduce mortality in patients with suspected or definite myocardial infarction. The mechanisms of action for these effects are not fully understood but may be related to a lower incidence of ventricular fibrillation and limitation of infarct size. Metoprolol has also been shown to reduce the incidence of recurrent myocardial infarction.

In cases of supraventricular tachycardia or atrial fibrillation, and in the presence of extrasystoles, metoprolol has a regulating effect on the heart rate.

Orthostatic reactions or disturbances of electrolyte balance have not been observed.

In therapeutic doses, metoprolol has less effect on the peripheral circulation and the bronchial muscles than non-selective β-blockers. However, metoprolol should be used with caution in patients with asthma, and concomitant use of an adrenergic bronchodilator, e.g., terbutaline or salbutamol, is advisable. Patients with reversible airways obstruction who are already taking β2-stimulants may require adjustment of the dosage of these if metoprolol therapy is subsequently introduced.

The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility, and cardiac output. Metoprolol tartrate will inhibit catecholamine induced lipolysis.

Metoprolol has also been shown to reduce diuretic induced increases in plasma renin activity. Metoprolol will inhibit catecholamine induced insulin secretion to a far lesser degree than non-selective β-blockers.

Metoprolol is practically devoid of membrane stabilising activity and does not display partial agonist activity (i.e., intrinsic sympathomimetic activity = ISA) at doses required to produce beta-blockade.

Metoprolol tartrate forms an active metabolite (2-hydroxymetoprolol) which does not, however, contribute significantly to the therapeutic effect.
Metoprolol is considered a relatively lipid soluble compound (i.e. less soluble than propranolol and more lipid soluble than atenolol).

Metoprolol has been shown to exert a prophylactic effect in both classical and common migraine.

**INDICATIONS**

- Hypertension
- Angina pectoris
- Suspected or definite myocardial infarction
- Migraine prophylaxis

**CONTRAINDICATIONS**

- Severe bronchial asthma or history of severe bronchospasm.
  β-Adrenergic blockade of the smooth muscle of bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

  Therefore, β-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm.

  Use of cardioselective β-blockers can also result in severe bronchospasm. Metoprolol should not be used in patients with severe bronchospastic disease (see PRECAUTIONS).

- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Right ventricular failure secondary to pulmonary hypertension.
- Significant right ventricular hypertrophy.
- Sinus bradycardia (less than 45 to 50 beats/min).
- Second and third degree atrioventricular block.
- Shock (including cardiogenic and hypovolaemic shock).
- Hypersensitivity to metoprolol tartrate.
- Hypersensitivity to any of the excipients in GenRx Metoprolol.
- Sensitivity to other β-blockers as cross sensitivity between β-blockers can occur.
- Non-compensated congestive heart failure (see PRECAUTIONS).
- Sick-sinus syndrome.
- Severe peripheral arterial circulatory disorders.
- Hypotension.
- Untreated phaeochromocytoma (see PRECAUTIONS).
- Myocardial infarction patients with a heart rate < 45 beats/min, a P-R interval of > 0.24 sec, a systolic blood pressure of < 100 mmHg, and/or moderate to severe heart failure.
PRECAUTIONS

Use with Caution in the Following Circumstances

Bronchospastic disease:
In general, patients with bronchospastic disease should not be given β-blockers of any type (e.g. selective or non-selective), including metoprolol. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

Cardiac Failure
β-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency, or unsuspected cardiomyopathy. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure are present, the patient should be fully digitised and/or given a diuretic and carefully monitored. If cardiac failure develops, GenRx Metoprolol should be discontinued gradually (see PRECAUTIONS, Abrupt Withdrawal).

β-blockers should not be used in patients with uncontrolled congestive heart failure; this condition should first be stabilised.

Note. Although congestive heart failure has been considered to be a contraindication to the use of β-blockers, there is growing literature on the experimental use of β-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, β-blockers should not normally be prescribed for heart failure outside specialist centres.

Myocardial Infarction
In patients with myocardial infarction, if significant hypotension occurs, metoprolol should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Intensive hemodynamic monitoring may be required and appropriate treatment modalities should be instituted. If hypotension is associated with significant bradycardia or atrioventricular block, treatment should be directed at reversing these.

Effects on the Heart Rate
If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/min) the dosage of metoprolol should be gradually reduced or treatment gradually withdrawn (see CONTRAINDICATIONS).

Abrupt Withdrawal
Care should be taken if β-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of β-blockade in patients with ischaemic heart disease. Therefore it is recommended that the dosage be reduced gradually over a period of 8 to 14 days during which time the patient’s progress should be assessed. GenRx Metoprolol should be temporarily re instituted if the angina worsens markedly or if acute coronary insufficiency develops. If the drug must be withdrawn abruptly in these patients, close observation is required. In the perioperative period, GenRx Metoprolol should not be withdrawn unless withdrawal is specifically indicated.

Peripheral Vascular Disease
β-Blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease. (see “CONTRAINDICATIONS”)

Prinzmetal Angina
There is a risk of exacerbating the number and duration of coronary artery spasm if patients with Prinzmetal angina or variant angina pectoris are treated with a β-blocker. If this treatment is essential, it should only be undertaken in a coronary or intensive care unit.

Diabetes
Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetes patients should be warned that β-Blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as
tachycardia. In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted. Diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.

Other Metabolic Effects
β-Adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

Phaeochromocytoma
In patients with this condition, or suspected of having this condition an α-blocking drug (e.g. phentolamine or phenoxybenzamine) should be administered before the β-blocker to avoid exacerbation of hypertension.

Effects on the Eye and Skin
Various rashes and conjunctival xerosis have been reported with β-blocking agents. Cross reactions may occur between β-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

During long-term treatment with the β-blocking drug practolol a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous or practolol syndrome. On a few rare occasions, serious otitis media, sclerosing peritonitis and pleurisy have been reported as part of this syndrome.

The oculomucocutaneous syndrome reported with practolol has not been reported with metoprolol. However, dry eyes and skin rash have been reported with metoprolol. In most cases the symptoms cleared when metoprolol was withdrawn. Patients should be observed carefully for potential ocular effects. If such symptoms occur, discontinuation of metoprolol should be considered.

More recently, an association between Peyronie’s disease (a fibrosing induration of the penis) and various β-blockers has been suggested but is not proven.

Allergic Conditions
Allergic reactions may be exaggerated by β-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). β-blockers should be avoided if there is a risk of bronchospasm.

In patients taking β-blockers, anaphylactic shock assumes a more severe form and may be resistant to normal doses of adrenaline. Whenever possible, β-blockers should be avoided in patients who are at increased risk of anaphylaxis.

Hyperthyroidism
Because β-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid status, special care should be exercised in hyperthyroid patients who are also receiving β-blockers. Where metoprolol is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

Effects on the Thyroid
The effects of β-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.
Renal Disease
In patients with severe renal disease, haemodynamic changes following β-blockade may impair renal function further. β-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

Conduction Disorders
Very rarely, a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). Metoprolol should be administered with caution to patients with first degree A-V block (see CONTRAINDICATIONS).

Hepatic Impairment
Metoprolol is mainly eliminated by means of hepatic metabolism (see PHARMACOLOGY, Pharmacokinetics). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations.

Women of child-bearing potential
Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor.

Use in Pregnancy (Category C)
β-blockers may reduce placental perfusion and cause bradycardia and hypoglycaemia in the foetus and newborn infant. During the later stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the foetus. The lowest possible dose should be used and treatment should be discontinued at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of β-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Animal studies have not demonstrated adverse maternal or foetal effects except in high doses in the rabbit, where slight reduction of litter size and slightly higher value of foetal loss were demonstrated.

There are few clinical data on the use of metoprolol tartrate during the first trimester of pregnancy. However, clinical experience suggests that in cases where its use is considered to be essential, metoprolol may be administered during pregnancy.

Metoprolol crosses the placental barrier in pregnant women; in one study the concentration in the umbilical vein was almost the same as in maternal vein plasma.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use in Lactation
Metoprolol is excreted in human breast milk. β-blockers taken by the mother may cause side effects, e.g. bradycardia, hypoglycaemia, in the breast-fed infant, although when the doses used are within the recommended therapeutic range, the very small amount of the drug ingested by the infant renders such effects unlikely. Experience suggests that metoprolol only need be discontinued during lactation if the infant’s hepatic function is severely impaired.

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

Use in the Elderly
Caution is indicated in elderly patients. An excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Effects on Ability to Drive or Use Machinery
Metoprolol may cause dizziness, fatigue or visual disturbances (see ADVERSE REACTIONS) and, therefore, may adversely affect the patient’s ability to drive or use machinery.
Interactions with Other Medicines

Other Antihypertensive Agents
Metoprolol enhances the effects of other antihypertensive drugs. Particular care is required when initiating administration of a β-blocker and prazosin together.

Sympathetic Ganglion Blocking Agents, Other β-blockers or Monoamine Oxidase (MAO) Inhibitors
Concomitant administration of sympathomimetic such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including, in antitussives or nose and eye drops) may provoke hypertensive reactions when used concomitantly with β-blockers; however, this is less likely with therapeutic doses of β₁-selective drugs than with non-selective β-blockers.

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β-blockers (including eye drops), or monoamine oxidase (MAO) inhibitors should be kept under close surveillance.

Anti-adrenergic agents Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by β-blockers. β-adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia.

Concurrent use of β-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the β-blocker. The rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a beta-blocker. If both drugs are withdrawn simultaneously, a marked rise in blood pressure, and/or arrhythmias may result.

Calcium Antagonists
The concomitant use of calcium antagonists with myocardial suppressant and sinus node activity (e.g. verapamil and to a lesser extent diltiazem) and β-blockers may cause bradycardia, hypotension and asystole. Extreme caution is required if these drugs have to be used together.

A calcium channel blocker of the phenylalkylamine type (i.e. verapamil) should not be administered intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation. Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium blocker of this type in combination with metoprolol should be closely monitored.

The combination of β-blockers with dihydropyridine calcium channel blockers with a weak myocardial effect (e.g. felodipine, nifedipine) can be administered together with caution. In case excess hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

Antiarrhythmic Drugs
β-blockers may enhance the negative inotropic and negative chronotropic effect of antiarrhythmic agents of the quinidine type.

Care should be taken when prescribing β-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant β-blocker therapy with the Class IA agents disopyramide, procainamide, ajmaline and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone (not available in Australia); the Class III agent, amiodarone; and the Class IV antiarrhythmic agents (e.g. verapamil). Particularly, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest, and atrioventricular block.

Digitalis / Digitalis Glycosides
Digitalis/digitalis glycosides and beta-blockers are commonly used together, although there have been reports of excessive bradycardia when beta-blockers are used to treat digitalis intoxication. Concurrent use may also result in an increase in atrioventricular conduction time. Monitoring heart rate and PR interval is recommended.
Glyceryl Trinitrate
Glyceryl trinitrate may enhance the hypotensive effect of metoprolol.

CYP2D6 Inhibitors
Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metaboliser. Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine, antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

Hydralazine: Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.

Non-steroidal anti-inflammatory drugs
Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors such as indomethacin with a β-blocker, may decrease the antihypertensive effect of metoprolol.

Alcohol
Metoprolol may modify the pharmacokinetic behaviour of alcohol when taken together. The plasma level of metoprolol may be raised by alcohol.

Liver Enzyme Effects
Enzyme-inducing and enzyme-inhibiting substances may change the plasma level of metoprolol. The plasma level of metoprolol is lowered by rifampicin and may be raised by cimetidine, alcohol and hydralazine and selective serotonin re-uptake inhibitors (SSRIs) e.g. paroxetine, fluoxetine and sertraline.

Antidiabetic Agents and Insulin
β-blockers may interfere with the usual haemodynamic response to hypoglycaemia and produce a rise in blood pressure associated with severe bradycardia. The dosages of antidiabetic medication may need to be adjusted in patients receiving β-blockers (see PRECAUTIONS).

Anaesthesia and the Perioperative Period
The necessity or desirability of withdrawing β-blocking agents prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anaesthesia and surgical procedures. The benefits of continuing a treatment with a β-blocker should be balanced against the risk of withdrawing it in each patient.

In patients receiving β-blocker therapy, inhalation anaesthetics may enhance the cardiodepressant effect. β-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance β-blockade be continued perioperatively. The anaesthetist must be made aware of β-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported.

Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of β-blockade. If it is thought necessary to withdraw β-blocker therapy before surgery, this should be done gradually and be completed about 48 hours before anaesthesia. (see PRECAUTIONS, Abrupt Withdrawal).

Metoprolol may also reduce the clearance of other drugs (e.g. lignocaine)
Warfarin
A limited number of reports have demonstrated a rise in AUC and concentration of warfarin when taken with another β-blocker. This could potentially increase the anticoagulant effect of warfarin.

Catecholamine Depleting Agents
Concomitant use of drugs such as reserpine and guanethidine requires careful monitoring since the added effect of a β-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

Ergot Alkaloid
Concomitant administration with β-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Dipyridamole
In general, administration of a β-blocker should be withheld before dipyridamole testing, with careful monitoring of heart rate following the dipyridamole injection.

ADVERSE EFFECTS
Occasionally, especially at the start of treatment, β-blockers may give rise to gastrointestinal upsets, sleep disturbances, or exertional tiredness. These effects however, are of a mild nature and seldom necessitate a reduction in the dosage.

The following events have been reported as adverse events in clinical trials or reported from routine use. In many cases a relationship with metoprolol has not been established. The following definitions of frequency are used: very common ≥ 10%; common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare < 0.01%.

Side effects reported in association with metoprolol tartrate treatment include the following:

Cardiovascular
Common: Bradycardia, postural disorders (very rarely with syncope), peripheral oedema, hypertension (mild and transient), cold hands and feet, arterial insufficiency, clinically significant falls in blood pressure after intravenous administration.

Uncommon: Transient deterioration of heart failure symptoms, A-V block I, cardiogenic shock in patients with acute myocardial infarction.*.

Rare: Cardiac failure, cardiac arrhythmias, palpitations, oedema, Raynaud’s phenomenon.

Very rare: Gangrene in patients with pre-existing severe peripheral circulatory disorders, angina (mild and transient), intermittent claudication, disturbances of cardiac conduction, precordial pain.

* Excess frequency of 0.4% compared with placebo in a study of 46000 patients with acute myocardial infarction where the frequency of cardiogenic shock was 2.3% in the metoprolol group and 1.9% in the placebo group in the subset of patients with low shock risk index. The shock risk index was based on the absolute risk of shock in each individual patient derived from age, sex, time delay, Killip class, blood pressure, heart rate, ECG abnormality, and prior history of hypertension. The patient group with low shock risk index corresponds to the patients in which metoprolol is recommended for use in acute myocardial infarction.

Central Nervous System
Common: Dizziness, headache, fatigue, tiredness.

Uncommon: Muscle cramps.

Rare: Depressed level of consciousness, paraesthesia.

Gastrointestinal
Common: Nausea, vomiting, abdominal pain, flatulence, heartburn, gastric pain.

Rare: Diarrhoea, constipation.
Very rare:  Dry mouth, retroperitoneal fibrosis (relationship to metoprolol has not been definitely established), unstable diabetes.

Haematologic

Rare:  Agranulocytosis.

Very rare:  Thrombocytopenia.

Hepatic

Very rare:  Hepatitis, liver function test abnormalities.

Metabolic

Very rare:  Weight gain.

Psychiatric

Uncommon:  Impaired concentrations

Rare:  Depression, nervousness, anxiety, impotence / sexual dysfunction, nightmares, somnolence or insomnia, short term memory loss.

Very rare:  Confusion, hallucinations, personality disorders.

Respiratory

Common:  Dyspnoea on exertion, dyspnoea.

Rare:  Bronchospasm (which may also occur in patients without a history of obstructive lung disease).

Very rare:  Rhinitis.

Sense Organs

Rare:  Conjunctivitis (see PRECAUTIONS).

Very rare:  Tinnitus, hearing disorders (e.g. hypoacusis or deafness - in doses exceeding those recommended), taste disturbances, disturbances of vision, dry and/or irritated eyes.

Skin

Common:  Pruritus, rash.

Rare:  Rash (in the form of urticaria, psoriasiform and dystrophic skin lesions.)

Very rare:  Photosensitivity reactions, aggravated psoriasis, hyperhidrosis, sweating increased, reversible alopecia.

Musculoskeletal, connective tissue disorders

Rare:  Muscle spasms.

Very rare:  Arthritis, musculoskeletal pain.

Reproductive system disorders

Very rare:  Erectile dysfunction, libido disorder and potency, Peyronie’s disease (relationship to metoprolol has not been definitely established).
Less Common Reactions (Frequency not Stated)

Hypotension.
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.

Potential Adverse Effects

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol.

Central Nervous System
Reversible mental depression progressing to catatonia; an acute reversible syndrome characterised by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance in neuropsychometrics.

Cardiovascular
Intensification of AV block (see "CONTRAINDICATIONS").

Haematologic
Nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitivity
Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

DOSAGE AND ADMINISTRATION

GenRx Metoprolol is recommended for oral therapy in hypertension, angina pectoris, suspected or definite myocardial infarction and migraine prophylaxis.

Hypertension

Initially
Mild hypertension: 50 or 100 mg, once daily for one week.

Severe hypertension: 50 or 100 mg, twice daily for one week.

Maintenance
50 or 100 mg, once or twice daily.

Some patients will respond to 50 mg once daily. However, a large number of patients will respond to 100 mg once daily as initial and maintenance therapy. Response is rarely improved by increasing the dose beyond 200 mg daily. The maximum daily dose should not exceed 400 mg. Although twice daily dosage is optimal in patients where maintenance dosage is 150 mg daily or less, it may be administered as a single dose.

Angina Pectoris
50 to 100 mg, two or three times daily.

Myocardial Infarction

Initially
Therapy should commence with Chemmart GenRx Terry White Chemists Metoprolol 50 mg tablets twice daily and be continued for 48 hours.
**Maintenance**
The oral maintenance dose is generally 100 mg twice daily.

**Migraine Prophylaxis**
100 to 150 mg, given in divided doses morning and evening.

**Paediatrics**
The safety and efficacy in children has not been established.

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**OVERDOSAGE**

**Symptoms**
Overdosage may lead to sinus bradycardia, severe hypotension, myocardial infarction, heart failure, bronchospasm, A-V block, cardiogenic shock, cardiac arrest, impairment of consciousness (even coma), convulsions, nausea, vomiting and cyanosis and death.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient’s condition.

The first signs of overdose can appear in 20 minutes after ingestion of tablets, but are more commonly seen within 1 to 2 hours. The effects of massive overdosage may persist for several days despite declining plasma concentrations.

**Treatment**
GenRx Metoprolol should be withdrawn.

The patient should be hospitalised so vital functions can be monitored. In general, patients with acute or recent myocardial infarction may be more haemodynamically unstable than other patients and should be treated accordingly.

Treatment should be symptomatic and supportive.

Induction of vomiting or gastric lavaging should be undertaken
Marked bradycardia and severe hypotension, and impending heart failure should be treated immediately with a β₁-stimulant (e.g. isoprenaline hydrochloride) intravenously at 2 to 5 minute intervals until the desired effect is achieved. Where a β₁-stimulant is not available, administer IV atropine 0.5 to 2 mg in order to block the vagus nerve. If a satisfactory response is not achieved, agents such as dopamine, dobutamine, or noradrenaline may be given.

Glucagon may also be given in a dose of 1 to 5 mg (maximum 10 mg). Glucagon activates the adenylcyclase system independently of the β-receptor, augmenting contractility in the presence of β-blockade. A pacemaker may be necessary.

Bronchospasm may necessitate administration of a β₂-stimulating agent (e.g. salbutamol) or intravenous aminophylline.

**Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.**
PRESENTATION AND STORAGE CONDITIONS

GenRx Metoprolol 50 mg Tablets:
Blister pack of 100 tablets.
AUST R number 78855

GenRx Metoprolol 100 mg Tablets:
Blister pack of 60 tablets.
AUST R number 78856

GenRx Metoprolol 50 mg and 100 mg Tablets are intended for oral administration. Each tablet contains metoprolol 50 mg or 100 mg.

In addition, each tablet contains the following inactive ingredients: lactose, maize starch, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, hydroxypropylcellulose, calcium hydrogen phosphate and crospovidone.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

GenRx is a registered trade mark of Apotex Pty Ltd.

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

Date of TGA approval: 22 May 2001

Date of most recent amendment: 2 July 2012