

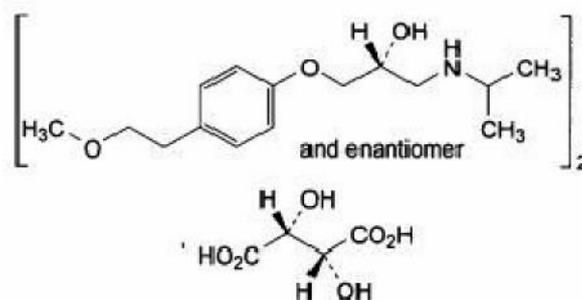
TERRY WHITE CHEMISTS METOPROLOL TABLETS

NAME OF THE MEDICINE

Metoprolol tartrate

Chemical Name: di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol] L(+)-tartrate

Structural Formula:



Molecular Weight: 684.81

Molecular Formula: $(C_{15}H_{25}NO_3)_2 \cdot (C_4H_6O_6)$

CAS number: 56392-17-7

DESCRIPTION

Metoprolol tartrate is a white, crystalline powder with a melting point of approximately 120°C. 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. Metoprolol tartrate is structurally related to other cardioselective β -blockers.

Each tablet contains either 50 mg or 100 mg of metoprolol tartrate as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose, colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, pregelatinised maize starch, sodium starch glycollate, magnesium stearate anhydrous, hypromellose, purified talc, macrogol 400 and titanium dioxide. The 50 mg strength tablets also contain iron oxide red.

PHARMACOLOGY

Pharmacotherapeutic group: cardio-selective β -blocker; ATC Code: C07A B02.

Pharmacological Actions

Metoprolol is a relatively cardioselective β -adrenoceptor blocking medicine without intrinsic sympathomimetic activity. It acts on β_1 -receptors mainly located in the heart at lower doses than those needed to influence the β_2 -receptors mainly located in the bronchi and peripheral vessels.

Metoprolol reduces the 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. This effect may possibly be attributable to a decrease in the incidence of severe ventricular

arrhythmias, as well as to 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 ventricular 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, it 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 on β_2 -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 will inhibit catecholamine-induced lipolysis.

Metoprolol has been shown to reduce diuretic-induced increase in plasma renin activity. It inhibits 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 β -blockade.

Metoprolol forms an active metabolite (2-hydroxymetoprolol), which does not 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.

Pharmacokinetics

Absorption

Metoprolol is rapidly and almost completely (more than 95%) absorbed from the gastro-intestinal tract. Metoprolol exhibits stereo-specific pharmacokinetics.

Distribution

Metoprolol is rapidly and extensively distributed to the extra-vascular tissue. The volume of distribution is 5.6 L/kg. At therapeutic concentrations, approximately 12 % of the active ingredient in Metoprolol tablets (metoprolol tartrate) is bound to human serum proteins.

Metabolism

Long-term studies have shown that metoprolol neither enhances nor inhibits its own metabolism. 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 metabolizers phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolisers. CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizers 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 medicine, caution should be exercised when administering metoprolol to poor metabolisers.

Excretion

Studies with 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. The elimination half-life of metoprolol is between 3 and 5 hours.

Metoprolol is excreted mainly by glomerular filtration.

Dose proportionality

Metoprolol exhibits saturable pre-systemic metabolism leading to non-proportionate increase in the exposure with increased dose.

Food effect

In a study in healthy volunteers (n=8), food significantly increased the extent of absorption of metoprolol after a single 100mg dose (p<0.05). The average increase in the plasma-concentration time AUC was 40% (range -28% to 132%). There was considerable variability. There was also a trend to higher and earlier peak plasma concentrations of metoprolol with food, although the differences compared with fasting were not significant. It is recommended that metoprolol be taken in standard relation to meals to minimise variations in effects (see **DOSAGE AND ADMINISTRATION**).

Dose-Response

The duration of the β -blocking effect is dose dependent (as measured by reduction of exercise heart rate). For instance, in healthy subjects the effect of 20 mg metoprolol given intravenously is halved after about 6 hours.

Pharmacokinetics in the Elderly

The geriatric population may show slightly higher plasma concentrations of metoprolol and the active metabolite α -hydroxymetoprolol than the young as a combined result of a decreased elimination of metoprolol and the metabolite in elderly population and a decreased hepatic blood flow. However, this increase is not clinically significant or therapeutically relevant. Whilst the pharmacokinetics of metoprolol are similar in the young and elderly, there may be pharmacodynamic changes in the elderly such as changes in the number of receptors or decreased receptor sensitivity; therefore, caution in dosing is recommended.

INDICATIONS

- Hypertension: as monotherapy or for use in combination with other antihypertensives.
- Angina pectoris: for long-term prophylaxis. Glyceryl trinitrate should be employed if necessary for alleviating acute attacks.
- Suspected or definite myocardial infarction.
- Migraine prophylaxis.

CONTRAINDICATIONS

- Bronchospasm β -adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These medicines 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. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.
- 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 45–50 beats/minute)
- Second or third degree atrioventricular (A-V) block
- Shock (including cardiogenic and hypovolaemic shock)
- Hypersensitivity to metoprolol, related derivatives or any of the excipients in metoprolol. Cross-sensitivity between β -blockers can occur. Congestive heart failure (see also **PRECAUTIONS**)
- Sick-sinus syndrome (unless a permanent, appropriately functioning pacemaker is in place)
- Severe peripheral arterial circulatory disorders

- Myocardial infarction patients with a heart rate of < 45 beats/min., a P-R interval of > 0.24 seconds, a systolic blood pressure of <100 mm Hg and/or moderate to severe heart failure
- Hypotension
- Untreated phaeochromocytoma (see **PRECAUTIONS**)
- Continuous or intermittent inotropic therapy acting through β -receptor agonism

PRECAUTIONS

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 digitalised and/or given a diuretic and carefully monitored. If cardiac failure persists, metoprolol should be discontinued gradually (see **PRECAUTIONS, Abrupt Withdrawal**).

β -blockers should not be used in patients with untreated congestive heart failure. This condition should first be stabilised. Although congestive heart failure has been considered to be a contraindication to the use of β -blockers, there is a growing literature on the experimental use of β -adrenergic blocking medicines in heart failure. As further trials are needed to identify which patients are most likely to respond to which medication, β -blockers should not normally be prescribed for heart failure outside of 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.

Prinzmetal Angina

There is a risk of exacerbating the number and duration of coronary artery spasms if patients with Prinzmetal angina or variant angina pectoris are treated with a β -blocker, including metoprolol. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

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**).

Phaeochromocytoma

In patients known to be, or suspected to be, suffering from a phaeochromocytoma, metoprolol should always be given in combination with an α -blocker (e.g. phentolamine or phenoxybenzamine) and only after the α -blocker has been initiated to avoid exacerbation of hypertension.

Diabetes

Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetic patients should be warned that β -blockers, including metoprolol, 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 adjustment. Diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.

Allergic Conditions

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

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

Hyperthyroidism

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

Peripheral Circulatory Disorders

β -blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (for example, Raynaud's disease or phenomenon, intermittent claudication) (see **CONTRAINDICATIONS**).

Renal Impairment

In patients with severe renal disease, haemodynamic changes following β -blockade may impair renal function further. Caution in metoprolol's dosing is recommended in patients with severe renal impairment. There is a possibility of accumulation of one of metoprolol's less active metabolites in patients with a creatinine clearance below 5 mL/min but this accumulation would not influence the β -blocking properties of metoprolol.

Hepatic Impairment

Metoprolol is mainly eliminated by means of hepatic metabolism (see **PHARMACOLOGY, Pharmacokinetics**). Therefore, liver cirrhosis may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Metoprolol blood levels are likely to increase substantially in patients with hepatic impairment. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h), in patients with liver impairment. Therefore, metoprolol should be initiated at low doses with cautious gradual dose titration according to clinical response.

Possible Effects of Treatment

Effects on the Heart Rate

If the patient develops increasing bradycardia (heart rate less than 50–55 beats/min), the dosage of metoprolol should be gradually reduced or treatment gradually withdrawn (see **CONTRAINDICATIONS**).

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.

Other Metabolic Effects

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

Effects on the Eye and Skin

Various skin 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 medicine, practolol, a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of the 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 syndrome or practolol syndrome. On a few rare occasions, serious otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported as part of this syndrome.

The oculomucocutaneous syndrome as 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 treatment 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.

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 about 8–14 days, during which time the patient's progress should be assessed. Metoprolol should be temporarily reinstated if the angina worsens.

If the medicine must be withdrawn abruptly in these patients, close observation is required. In the peri-operative period metoprolol should not be withdrawn, unless withdrawal is specifically indicated.

Effects on Fertility

The effects of metoprolol on the fertility of humans have not been studied. While metoprolol showed reversible adverse effects on spermatogenesis (altered morphology and motility) in male rats at less than therapeutic doses, it had no effect on rates of conception in animal fertility studies at up to 11 times the maximum recommended daily dose on a body surface area adjusted basis.

Use in Pregnancy (Category C)

Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor.

Metoprolol has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the foetus when metoprolol is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly indicated.

Experience with metoprolol in the first trimester of pregnancy is limited, but no foetal malformations attributable to metoprolol have been reported. In general, no drug should be taken during the first 3 months of pregnancy, and the relative benefits and risks of treatment should be carefully considered throughout pregnancy.

There is a limited amount of data on the use of metoprolol in pregnant women. Experiences with metoprolol in the first trimester of pregnancy is limited, but no foetal malformations attributable to metoprolol have been reported.

β -blockers may reduce placental perfusion and cause bradycardia in the foetus and newborn infant. 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.

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 discontinuation of treatment should be considered at least 2–3 days before delivery to avoid increased uterine contractility and effects of β -blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Use in Lactation

The concentration of metoprolol in breast milk is approximately three times higher than in the mother's plasma. However, in the normal dose range, the amount of metoprolol ingested via human milk seems to be negligible with regard to its β -blocking effect on the infant. Nevertheless, breast-fed infants should be closely observed for signs or symptoms of β -blockade. Experience suggests that metoprolol only need to be discontinued during lactation if the infant's hepatic function is severely impacted.

Paediatric Use

No paediatric studies have been performed. The safety and efficacy in paediatric patients have not been established.

Use in the Elderly

Caution in dosing is recommended due to increased likelihood of adverse events (see **PHARMACOLOGY - PHARMACOKINETICS IN THE ELDERLY**).

Genotoxicity

Metoprolol was devoid of mutagenic/genotoxic potential in the bacterial cell system (Ames) test and *in vivo* assays involving mammalian somatic cells or germinal cells of male mice.

Carcinogenicity

Metoprolol was not carcinogenic in mice and rats after oral administration of doses up to 800 mg/kg for 21–24 months.

Effects on the Ability to Drive and Operate Machinery

Metoprolol may cause dizziness, fatigue or visual disturbances (see **ADVERSE EFFECTS**) and, therefore, may adversely affect the patient's ability to drive or use machinery.

INTERACTIONS WITH OTHER MEDICINES**Antiarrhythmic Medicines**

β -blockers may enhance the negative inotropic and negative chronotropic effect of anti-arrhythmic agents of the quinidine type. Care should be taken when prescribing β -blockers with antiarrhythmic medicines. Interactions have been reported during concomitant β -blocker therapy with the Class IA agents, disopyramide and less frequently, quinidine; Class IB agents, lignocaine; Class IC agents, flecainide and propafenone (not available in Australia); the Class III agent, amiodarone; and the Class IV 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.

Sympathetic Ganglion Blocking Agents, other β -blockers or Monoamine Oxidase (MAO) Inhibitors

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β -blockers (also in the form of eye drops) or monoamine oxidase (MAO) inhibitors should be kept under surveillance. Possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

Antihypertensive Medicines

Metoprolol enhances the effect of other antihypertensive medicines. Particular care is required when initiating administration of a β -blocker and prazosin together.

Anti-adrenergic agents

Antihypertensive effect of α -adrenergic blockers such as guanethidine, betanidine, reserpine, α -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.

Clonidine

Concurrent use of β -blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If concomitant treatment with clonidine is to be discontinued, the β -blocker medication should be withdrawn several days before clonidine. The rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a β -blocker. If both medicines are withdrawn simultaneously, a marked rise in blood pressure and/or arrhythmias may result.

Catecholamine-depleting Agents

Concomitant use of medicines 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.

Calcium Antagonists

The concomitant use of β -blockers and calcium antagonists with myocardial depressant and sinus node activity, e.g. verapamil and to a lesser extent diltiazem, may cause hypotension, bradycardia and asystole. Extreme caution is required if these medicines have to be used together. A calcium channel blocker of the phenylalkylamine type (e.g. 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 β -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 channel 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 depressant effect (e.g. felodipine, nifedipine) can be administered together with caution. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

Prostaglandin Synthetase Inhibiting Agents

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of β -blockers.

Alcohol

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

Hepatic Enzyme Effects

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

Oral Antidiabetic Agents

β -blockers may interfere with the usual haemodynamic response to hypoglycaemia and produce a rise in blood pressure associated with severe bradycardia. When treating diabetics with β -blockers, caution is indicated and the dosage of antidiabetic medication may need to be adjusted.

Anaesthetics

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.

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 peri-operatively. The anaesthetist must be made aware of β -blockade because of the potential for interactions with other medicines, 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.

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.

Inhalation anaesthetics may enhance the cardio-depressant effect of β -blocker therapy. 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 completed about 48 hours before surgery (see **PRECAUTIONS, Abrupt Withdrawal**).

Metoprolol may reduce the clearance of other medicines (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 anti-coagulant effect of warfarin.

Digitalis Glycosides

Digitalis glycosides, in association with β -blockers, may increase atrioventricular conduction time and may induce bradycardia. Monitoring of the heart rate and PR interval is recommended.

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 SSRIs (see **Hepatic Enzyme Effects**) or bupropion, clomipramine, 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.

Glyceryl Trinitrate

Glyceryl Trinitrate may enhance the hypotensive effect of metoprolol.

Sympathomimetics

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 β_1 -selective medicines than with non-selective β -blockers.

A watch should be kept for possible negative inotropic and chronotropic effects when metoprolol is given together with calcium antagonists and/or anti-arrhythmic agents.

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 gastro-intestinal upsets, sleep disturbances or exertional tiredness. These effects, however, are of a mild nature and seldom necessitate a reduction in the dosage.

Cardiovascular adverse effects (related, possibly related, unassessable or unknown) reported by $\geq 1\%$ in 1,395 patients during randomised clinical trials of metoprolol and placebo:

	Metoprolol	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

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: $\geq 10\%$;

Common: $\geq 1\%$ and $< 10\%$;

Uncommon: $\geq 0.1\%$ and $< 1\%$;

Rare: $\geq 0.01\%$ and $< 0.1\%$;

Very rare: $< 0.01\%$.

Central Nervous System

Common: dizziness, headache

Uncommon: paraesthesia

Rare: depressed level of consciousness

Cardiovascular

Common: bradycardia, palpitations

Rare: transient deterioration of heart failure symptoms, A-V block I, oedema, precordial pain, cardiogenic shock in patients with acute myocardial infarction*, cardiac arrhythmias

Very rare: conduction disorders

* 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.

Gastrointestinal disorders

Common: nausea and vomiting, diarrhoea, constipation abdominal pain, heartburn, flatulence, gastric pain

Rare: dry mouth

Very rare: retroperitoneal fibrosis (relationship to metoprolol has not been definitely established), unstable diabetes

Haematological

Rare: agranulocytosis

Very rare: thrombocytopenia

Hepatobiliary disorders

Rare: liver function test abnormalities

Very rare: hepatitis

Immune System disorders

Hypersensitivity

Musculoskeletal, Connective Tissue disorders

Uncommon: muscle cramps
Rare: muscle spasms
Very rare: arthritis, musculoskeletal pain

Metabolic

Uncommon: weight gain

Psychiatric disorders

Uncommon: depression, impaired concentration, somnolence or insomnia, nightmares
Rare: nervousness, anxiety
Very rare: personality disorder, hallucinations, mental confusion, amnesia / memory impairment

Respiratory

Common: dyspnoea, dyspnoea on exertion
Rare: bronchospasm (which may occur in patients without a history of obstructive lung disease)
Very rare: rhinitis

Reproductive System

Very rare: erectile dysfunction, libido disorder and potency, Peyronie's disease (relationship to metoprolol has not been definitely established)

Sense Organs

Rare: disturbances of vision, dry eyes and/or eye irritation, conjunctivitis
Very rare: tinnitus, hearing disorders when exceeding recommended doses (e.g. hypoacusis or deafness), taste disturbances

Skin

Common: pruritus, rash
Uncommon: rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), increased sweating
Rare: reversible alopecia
Very rare: photosensitivity reaction, hyperhidrosis, aggravation of psoriasis

Vascular disorders

Common: postural disorders (occasionally with syncope), clinically significant falls in blood pressure after intravenous administration, peripheral oedema, hypertension (mild and transient), cold hands and feet (Raynaud's phenomenon), arterial insufficiency
Rare: oedema
Very rare: gangrene in patients with pre-existing severe peripheral circulatory disorders, angina (mild and transient), intermittent claudication

General disorders

Very common: fatigue
Common: tiredness

Post-marketing Data – Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

In addition to the adverse events reported in the clinical trials, the following events have been reported during post-marketing surveillance of metoprolol*:

Nervous System disorders

Confusional state.

Investigations

Increase in blood triglycerides, 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 Reactions

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

Cardiac disorders

Intensification of AV block (see **CONTRAINDICATIONS**).

Blood and the Lymphatic System disorders

Non-thrombocytopenic purpura, thrombocytopenic purpura.

Nervous System disorders

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.

Hypersensitivity Reactions

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

DOSAGE AND ADMINISTRATION

The maximum daily dose should not exceed 400 mg.

Although twice daily dosage is optimal, in those patients whose maintenance dosage is 150 mg daily or less, it may be administered as a single dose.

It is advisable to individualise the dosage.

The film coated tablets should be swallowed whole.

Hypertension

Mild: 50 or 100 mg, given once daily, for one week

Moderate to severe: 50 or 100 mg, given twice daily for one week

Maintenance: 50 or 100 mg, given once or twice daily.

Some patients may respond to 50 mg once daily. However, a large number of patients will respond to 100 mg, given once daily as initial and maintenance therapy. Response is rarely improved by increasing the dose beyond 200 mg daily.

Angina Pectoris

50 mg to 100 mg, given two or three times daily

Myocardial Infarction

The recommended dosage can be reduced depending on the haemodynamic status of the patient.

Initially

Therapy should commence with 50 mg twice daily and be continued for 48 hours.

Maintenance

Generally 100 mg, given twice daily.

Migraine Prophylaxis

100 to 150 mg, given in two divided doses (morning and evening).

OVERDOSAGE**Symptoms**

Poisoning due to an overdosage of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting and cyanosis and death.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates aggravates the signs and symptoms.

The first manifestations of overdosage can appear in 20 minutes but are more commonly seen within 1–2 hours after the drug's ingestion. The effects of massive overdosage may persist for several days despite declining plasma concentrations.

Treatment

Patients suffering from overdosage of a β -blocker should always be hospitalised so that 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.

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

In the presence of severe hypotension, bradycardia and impending heart failure, administer a β_1 -stimulant (e.g. isoprenaline) intravenously at 2–5 minute intervals until the desired effect is achieved. Where a β_1 -stimulant is not available, administer 0.5–2.0 mg atropine sulphate i.v. in order to block the vagus nerve. If a satisfactory effect is not achieved, agents such as dopamine, dobutamine or noradrenaline may be administered.

Further measures: 1–5 (max. 10) mg glucagon (glucagon activates the adenylyclase system independently of the β -receptor, augmenting contractility in the presence of β -blockade); transvenous intracardiac pacemaker. To combat bronchospasm, a β_2 -stimulant (e.g. salbutamol) or aminophylline can be given intravenously.

For information on management on overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Terry White Chemists Metoprolol tablets are intended for oral administration.

Each tablet contains 50 mg or 100 mg metoprolol tartrate as the active ingredient.

50 mg tablet:

Pink, round, biconvex film-coated tablets with 'B' and 'L' separated by a notch break line on one side and '50' debossed on other side.

Blister packs (PVC/Aluminium silver foil) of 10 or 100 tablets (AUST R 210514).

100 mg tablet:

White to off-white, round, biconvex film-coated tablets with 'B' and 'L' separated by a notch break line on one side and '100' debossed on other side.

Blister packs (PVC/Aluminium silver foil) of 10 or 60 tablets (AUST R 210515).

Not all strengths or pack sizes may be available.

Storage

Store below 30°C. Protect from light and moisture, store in the original packaging.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

8 January 2013

DATE OF MOST RECENT AMENDMENT

22 July 2016