

AUSTRALIAN PRODUCT INFORMATION

MINAX[®]

(metoprolol tartrate) tablet



1 NAME OF THE MEDICINE

Metoprolol tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MINAX 50 tablet contains 50 mg of metoprolol tartrate as the active ingredient.

Each MINAX 100 tablet contains 100 mg of metoprolol tartrate as the active ingredient.

Excipients with known effects: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

MINAX 50 : White, round tablet, marked "ML|50" on one side, "α" on the reverse.

MINAX 100 : White, round tablet, marked "ML|100" on one side, "α" on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.
- Confirmed or suspected myocardial infarction
- Prevention of migraine.

4.2 DOSE AND METHOD OF ADMINISTRATION

It is advisable to individualise the dosage.

Hypertension

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

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

Maintenance: 50 or 100 mg once or twice daily. Some patients may respond to 50 mg once daily. A larger number 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 those patients whose maintenance dosage is 150 mg daily or less, it may be administered as a single dose.

Angina pectoris

50 mg to 100 mg 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 twice daily.

Prevention of migraine

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

4.3 CONTRAINDICATIONS

- Bronchospasm.

Beta-adrenergic blockade of the smooth muscle of bronchi and 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. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

- Hypersensitivity to metoprolol tartrate, related derivatives, or any of the excipients in MINAX.
- Sensitivity to other β -blockers (cross-sensitivity between β -blockers can occur).
- Second and third degree atrioventricular block.
- Non-compensated congestive heart failure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Sinus bradycardia (less than 45 to 50 beats/minute).
- Sick-sinus syndrome (unless a permanent, appropriately functioning pacemaker is in place).
- Severe peripheral arterial circulatory disorders.
- Shock (including cardiogenic and hypovolaemic shock).
- Myocardial infarction patients with a heart rate of < 45 beats/minute, a P-R interval of > 0.24 seconds, a systolic blood pressure of <100 mmHg, and/or moderate to severe non-compensated heart failure.
- Right ventricular failure secondary to pulmonary hypertension.
- Significant right ventricular hypertrophy.
- Hypotension.
- Untreated pheochromocytoma (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Continuous or intermittent inotropic therapy acting through beta receptor agonism.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bronchospastic disease

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

Cardiac failure

Beta-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 tartrate should be discontinued gradually (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Abrupt withdrawal).

Beta-blockers should not be used in patients with untreated 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 a 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 of specialist centres).

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a β -blocker. 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). MINAX should be administered with caution to patients with first degree A-V block (see Section 4.3 CONTRAINDICATIONS).

Phaeochromocytoma

In patients with phaeochromocytoma, an alpha-blocker (e.g. phentolamine or phenoxybenzamine) should be administered before the β -blocker to avoid exacerbation of hypertension.

Diabetes

MINAX 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 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 MINAX should be monitored to ensure that diabetes control is maintained.

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). Beta-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(epinephrine). Whenever possible, β -blockers 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 MINAX is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

Peripheral vascular disease

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see Section 4.3 CONTRAINDICATIONS).

Use in Hepatic Impairment

Metoprolol is mainly eliminated by means of hepatic metabolism (see Section 5.2 PHARMACOKINETIC PROPERTIES). Therefore, liver cirrhosis may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations.

Use in Renal Impairment

In patients with severe renal disease, haemodynamic changes following β -blockade may impair renal function further. Beta-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

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.

Concomitant therapy with 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 drugs 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. 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. In case excess hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

Antiarrhythmic drugs

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, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lidocaine(lignocaine); Class IC agents, flecainide and propafenone (not available in Australia); the Class III agent amiodarone; and the class IV agents (e.g. verapamil).

Clonidine

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.

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.

General anaesthetics

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative 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 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.

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.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Abrupt Withdrawal).

Effects on the heart rate

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/ minute), the dosage of MINAX should be gradually reduced or treatment gradually withdrawn (see Section 4.3 CONTRAINDICATIONS).

Effects on the thyroid

The effects of β -blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) 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

Beta-adrenoceptors 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.

Effects on the eye and skin

Various rashes and conjunctival xeroses 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 syndrome or practolol syndrome. On a few rare occasions, serous otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported.

The oculomucocutaneous syndrome as reported with practolol has not been reported with metoprolol. However, dry eyes and skin rash have been reported with metoprolol. 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. MINAX should be temporarily reinstated if the angina worsens.

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

Paediatric Use

The safety and efficacy in children have not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Other anti-hypertensive agents

Metoprolol enhances the effect of other antihypertensive drugs. Particular caution is required when administering a β -blocker and prazosin together for the first time.

Sympathetic ganglion blocking agents, other beta-blockers or monoamine oxidase (MAO) inhibitors

Patients receiving concurrent treatment with sympathetic ganglion blocking agents, other β -blockers (including eye drops), or monoamine oxidase (MAO) inhibitors should be carefully monitored.

Clonidine

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 drugs are withdrawn simultaneously, marked rise in blood pressure, and/or arrhythmias may result.

Calcium antagonists

When metoprolol is given together with calcium antagonists of the verapamil and diltiazem type and/or anti-arrhythmic agents, the patient should be monitored for possible negative inotropic and chronotropic effects. Calcium antagonists of the verapamil type should not be given by intravenous administration to patients treated with β -blockers.

Anti-arrhythmic agents

When metoprolol is given together with anti-arrhythmic agents the patient should be monitored for possible negative inotropic and chronotropic effects. The negative inotropic and negative chronotropic effects of antiarrhythmic agents of the quinidine type and amiodarone may be enhanced by beta-blockers.

Prostaglandin synthetase inhibiting agents

Concurrent treatment with 7ndomethacin 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.

Liver enzyme effects

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

Oral antidiabetic agents

The dosage of oral antidiabetics may need to be adjusted in patients receiving β -blockers (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Anaesthetics

Inhalation anaesthetics enhance the cardiodepressant effect of β -blocker therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Metoprolol may also reduce the clearance of other drugs (e.g. lidocaine(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.

Digitalis glycosides

Digitalis glycosides, in association with beta blockers, may increase atroventricular conduction time and may induce bradycardia.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: C

Metoprolol should not be given during pregnancy unless its use is considered essential. In general, β -blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofetal monitoring be performed in pregnant women treated with metoprolol.

Beta-blockers may 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 to 3 days before delivery to avoid increased uterine contractility and effects of β -blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Use in Lactation

Metoprolol is excreted in human breast milk. Beta-blockers taken by the mother may cause side-effects, e.g. bradycardia, in the breast fed infant, although when the doses used are within the recommended therapeutic range, the very small amount of drug ingested by the infant renders such effects unlikely. Nevertheless, breastfed infants should be closely observed for signs or symptoms of β -blockade.

Experience suggests that metoprolol only need be discontinued during lactation if the infant's hepatic function is severely impaired.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINAX may cause dizziness, fatigue or visual disturbances (see Section 4.8 ADVERSE EFFECTS (Undesirable effects)) and, therefore, may adversely affect the patient's ability to drive or use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Occasionally, especially at the start of treatment, beta-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.

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 1 – 9.9%; uncommon 0.1 – 0.9%; rare 0.01 – 0.09%; very rare $< 0.01\%$.

Cardiovascular

Common: bradycardia, postural disorders (very rarely with syncope), cold hands and feet (Raynaud's phenomenon), palpitations, clinically significant falls in blood pressure after intravenous administration.

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

Rare: disturbances of cardiac conduction, cardiac arrhythmias.

Very rare: gangrene in patients with pre-existing severe peripheral circulatory 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.

Central nervous system

Very common: fatigue

Common: dizziness, headache.

Uncommon: paraesthesia, muscle cramps.

Gastrointestinal

Common: nausea, diarrhoea, constipation, abdominal pain.

Uncommon: vomiting.

Rare: dry mouth.

Haematologic

Very rare: thrombocytopenia.

Hepatic

Rare: liver function test abnormalities.

Very rare: hepatitis

Metabolic

Uncommon: weight gain.

Psychiatric

Uncommon: depression, impaired concentration, somnolence or insomnia, nightmares.

Rare: nervousness, anxiety, impotence / sexual dysfunction.

Very rare: amnesia / memory impairment, confusion, hallucinations.

Respiratory

Common: dyspnoea on exertion.

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

Rare: rhinitis.

Sense organs

Rare: disturbances of vision, dry and/or irritated eyes, conjunctivitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Very rare: tinnitus, taste disturbances.

Skin

Uncommon: rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), increased sweating.

Rare: loss of hair

Very rare: photosensitivity reactions, aggravated psoriasis.

Miscellaneous

Very rare: arthralgia

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Symptoms of overdosage may include severe hypotension, cardiac insufficiency, bradycardia and bradyarrhythmia, cardiac conduction disturbances, cardiogenic shock, cardiac arrest, impairment of consciousness/coma, convulsions and bronchospasm. The main clinical signs of overdosage are cardiovascular and in some cases decompensation may be rapid. Overdosage with MINAX can lead to death.

Cases of overdosage in paediatric patients need to be given extra attention even if the patient appears well on presentation and even if only a small number of tablets have apparently been taken.

Management

Care should be provided at a facility that can provide appropriate supporting measures, monitoring, and supervision.

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Syrup of ipecac and gastric lavage are no longer considered to be standard therapy for gut decontamination.

Atropine, adreno stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension, acute cardiac failure, and shock to be treated with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adreno stimulating drugs such as dobutamine, with α_1 receptor agonistic drugs added in presence of vasodilation. Intravenous use of calcium salts (Ca^{2+}) can also be considered.

Bronchospasm can usually be reversed by bronchodilators.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Metoprolol is a relatively cardioselective beta-adrenoceptor blocking drug without intrinsic sympathomimetic activity, and is suited for the treatment of hypertension. 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 decreases 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 of metoprolol 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 peripheral circulation and the bronchial muscles than nonselective 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 recommended. Patients already taking β_2 -stimulants for reversible airways obstruction may require adjustment of 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 inhibits 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 nonselective β -blockers.

Metoprolol is practically devoid of membrane-stabilising activity, 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, 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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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 tissue. The volume of distribution is 5.6 L/kg. At therapeutic concentrations approximately 12% of metoprolol is bound to human serum proteins.

Metabolism and Excretion

Studies with radioactively labelled drug have shown that more than 90% of the dose is excreted in the urine in 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 is between 3 and 5 hours.

Dose-response

The duration of the β -blocking effects 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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

MINAX 50 tablets contain lactose monohydrate, microcrystalline cellulose, povidone, colloidal anhydrous silica, sodium starch glycollate and magnesium stearate.

MINAX 100 tablets contain lactose monohydrate, microcrystalline cellulose, povidone, purified talc, colloidal anhydrous silica, sodium starch glycollate, carmellose sodium and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Blister pack : Store below 30°C.

Bottle : Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

MINAX 50 : Pack sizes: Available in PVC/PVDC/Al blister and HDPE bottle packs of 100's.

MINAX 100 : Pack sizes: Available in PVC/PVDC/Al blister and HDPE bottle packs of 60's.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 34408 – MINAX 50 metoprolol tartrate 50 mg tablet bottle.

AUST R 34410 – MINAX 100 metoprolol tartrate 100 mg tablet bottle.

AUST R 42749 - MINAX 50 metoprolol tartrate 50 mg tablet blister pack.

AUST R 42750 - MINAX 100 metoprolol tartrate 100 mg tablet blister pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

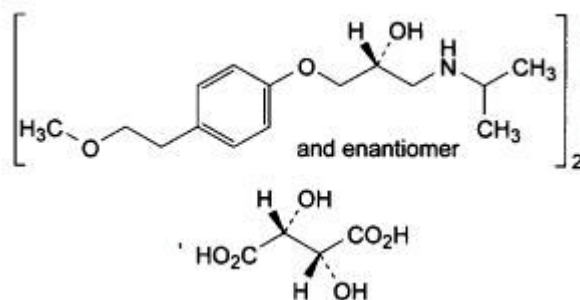
6.7 PHYSICOCHEMICAL PROPERTIES

Metoprolol tartrate, an aryloxypropanolamine derivative, is a white crystalline powder with a melting point of 120°C. The powder is odourless or almost odourless. It is very soluble in water, soluble in chloroform, methylene chloride and alcohol, and almost insoluble in benzene, diethylether and acetone.

Chemical Structure

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

Structural formula :



Molecular formula : $(C_{15}H_{25}NO_3)_2, C_4H_6O_6$ Molecular weight : 685

CAS Number

56392-17-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

MINAX 100 tablet blister pack: 23/11/1992

MINAX 50 tablet blister pack: 23/11/1992

MINAX 100 tablet bottle: 24/11/1992

MINAX 50 tablet bottle: 24/11/1992

10 DATE OF REVISION

03/08/2023

Summary Table of Changes

Section Changed	Summary of New Information
2, 3	Minor editorial changes
6.5	Insert AUST R numbers
8	Update to sponsor details

MINAX® is a Viartis company trade mark

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