

# AUSTRALIAN PRODUCT INFORMATION

## **BETALOC® Metoprolol Tartrate**

### **1 NAME OF THE MEDICINE**

Metoprolol tartrate.

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

BETALOC tablets contain 50 mg or 100 mg metoprolol tartrate and the following inactive ingredients: lactose monohydrate, cellulose microcrystalline, colloidal anhydrous silica, sodium starch glycollate, povidone and magnesium stearate.

BETALOC Injection solution contains 1mg/mL metoprolol tartrate and the following inactive ingredients: sodium chloride and water for injections.

### **3 PHARMACEUTICAL FORM**

#### **Tablets 50 mg**

White to off-white, circular, biconvex tablet with a diameter of 8 mm, scored and marked A/BB on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

#### **Tablets 100 mg**

White to off-white, circular, biconvex tablet with a diameter of 10 mm, scored and marked A/ME on one side. The tablet can be divided into equal halves.

#### **Injection solution, 1mg/mL**

Clear, colourless liquid.

### **4 CLINICAL PARTICULARS**

#### **4.1 THERAPEUTIC INDICATIONS**

##### **Oral therapy**

- Hypertension
- angina pectoris prophylaxis
- suspected or definite myocardial infarction
- migraine prophylaxis.

##### **Intravenous therapy**

- disturbances of cardiac rhythm, in particular supraventricular tachyarrhythmias.

## **4.2 DOSE AND METHOD OF ADMINISTRATION**

### **Oral Therapy**

BETALOC (metoprolol tartrate) is recommended for oral therapy in hypertension, angina pectoris, suspected or definite myocardial infarction and migraine prophylaxis.

BETALOC 50 mg tablets are scored to facilitate breaking for ease of swallowing only and not to divide the tablet into equal doses. BETALOC 100 mg tablets can be divided into two equal doses.

### ***Hypertension***

#### ***Initially***

Mild hypertensives:

50 or 100 mg once daily, for one week.

Severe hypertensives:

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 dose is 150 mg daily or less, it may be administered as a single dose.

### ***Angina Pectoris***

50 - 100 mg two or three times daily.

### ***Myocardial Infarction***

#### ***Initially***

Therapy should commence with BETALOC (metoprolol tartrate) tablets 50 mg twice daily and be continued for 48 hours.

#### ***Maintenance***

The oral maintenance dose is generally 100 mg twice daily.

### ***Migraine Prophylaxis***

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

### **Intravenous Therapy**

BETALOC (metoprolol tartrate) injection is suitable for the treatment of disturbances of cardiac rhythm, particularly supraventricular tachyarrhythmias (see Section 5 – Pharmacological properties).

Initially, up to 5 mg is given at a rate of 1 to 2 mg per minute. This dose may be repeated at 5-minute intervals until a satisfactory effect is achieved. A total dose of 10 to 15 mg will generally produce a satisfactory effect. Doses of 20 mg or more are unlikely to result in further therapeutic benefit. Blood pressure and ECG should be monitored during the treatment.

Parenteral administration should be conducted by experienced staff with suitable monitoring and resuscitating equipment available.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

### **Paediatric Use**

The safety and efficacy in children have not been established.

### **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, beta-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective beta 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 and third degree A-V block
- Shock (including cardiogenic and hypovolaemic shock)
- Hypersensitivity to metoprolol tartrate, related derivatives, or any of the excipients in BETALOC. Cross-sensitivity between beta-blockers can occur.
- Non-compensated congestive heart failure (see Section 4.4 Special warnings and precautions for use).
- 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/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

- Hypotension
- Untreated phaeochromocytoma (see Section 4.4 Special warnings and precautions for use)
- Continuous or intermittent inotropic therapy acting through  $\beta$ -receptor agonism

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

##### **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, BETALOC (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 beta-blockers, there is growing literature on the experimental use of beta-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, beta-blockers should not normally be prescribed for heart failure outside specialist centres.)

##### **Prinzmetal angina**

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

##### **Phaeochromocytoma**

In patients with this condition, an alpha-blocking drug (e.g. phentolamine/phenoxybenzamine) should be administered before the beta-blocker to avoid exacerbation of hypertension.

##### **Diabetes**

BETALOC 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 beta-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, beta-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 BETALOC should be monitored to ensure diabetes control is maintained.

### **Allergic conditions**

Allergic reactions may be exaggerated by beta-blockade (eg. 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 beta-blockers, anaphylactic shock assumes a more severe form and may be resistant to normal doses of adrenaline. Whenever possible, beta-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 also receiving beta-blockers because beta-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid status. Where BETALOC is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be closely monitored.

### **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 renal impairment**

In patients with severe renal disease, haemodynamic changes following beta-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 hepatic impairment**

Metoprolol is mainly eliminated by 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 levels.

### **Intravenous therapy**

The intravenous administration of metoprolol tartrate to patients with a systolic blood pressure below 100 mmHg (13.3 kPa) should be carried out with special care as it can result in a further significant decrease of blood pressure.

### **Concomitant therapy with calcium antagonists**

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

A calcium antagonist 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 oral calcium antagonists of this type in combination with metoprolol should be closely monitored.

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

### **Clonidine**

Concurrent use of beta-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 beta-blocker.

### **Antiarrhythmic drugs**

Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, 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).

### **Catecholamine depleting agents**

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

### **General anaesthesia**

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 beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-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 beta-blockade. If it is thought necessary to withdraw beta-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 BETALOC should be gradually reduced or treatment gradually withdrawn (see Section 4.3 Contraindications).

### **Effects on the thyroid**

The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T<sub>4</sub>) 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 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.

### **Effects on the eye and skin**

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

During long-term treatment with the beta-blocking drug 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 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 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 beta-blockers has been suggested but is not proven.

### **Abrupt withdrawal**

Care should be taken if beta-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 beta-blockade in patients with ischaemic heart disease.

Therefore, it is recommended that the dosage be reduced gradually over a period of 8-14 days during which time the patient's progress should be assessed. BETALOC 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 BETALOC (metoprolol tartrate) should not be withdrawn, unless withdrawal is specifically indicated.

### **Use in the elderly**

See Section 5.2 Pharmacokinetic properties – Pharmacokinetics in the elderly.

### **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 effects of other antihypertensive drugs. Particular care is required when initiating administration of a beta-blocker and prazosin together.

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

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

### **Clonidine**

If concomitant treatment with clonidine is to be discontinued, the beta-blocker medication should be withdrawn several days before clonidine. 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**

When metoprolol is given together with calcium antagonists of the verapamil and diltiazem type 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 beta-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**

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



## **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, hydralazine and selective serotonin re-uptake inhibitors (SSRI's) eg paroxetine, fluoxetine and sertraline.

## **Oral antidiabetic agents**

The dosages of oral antidiabetics may need to be adjusted in patients receiving beta-blockers. (see Section 4.4 Special warnings and precautions for use).

## **Anaesthetics**

Inhalation anaesthetics enhance the cardiosuppressant effect of beta-blocker therapy (see Section 4.4 Special warnings and precautions for use). 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 beta-blocker. This could potentially increase the anti-coagulant effect of warfarin.

## **Digitalis glycosides**

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

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

No data available.

### **Use in pregnancy – Category C**

BETALOC should not be given during pregnancy unless its use is considered essential. In general,  $\beta$ -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 new-born 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 late 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 beta-blockade in the newborn (eg. 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.

Experience suggests that BETALOC (metoprolol tartrate) 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**

BETALOC may cause dizziness, fatigue or visual disturbances (see Section 4.8 Adverse 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](http://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 BETALOC 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**

For information on management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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  $\alpha_1$  receptor agonistic drugs added in presence of vasodilation. Intravenous use of calcium salts ( $\text{Ca}^{2+}$ ) can also be considered.

Bronchospasm can usually be reversed by bronchodilators.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

BETALOC (metoprolol tartrate) is a relatively cardioselective beta adrenoceptor blocking drug without intrinsic sympathomimetic activity, and is suited for the treatment of hypertension. It acts on  $\beta_1$ - receptors mainly located in the heart at lower doses than those needed to influence the  $\beta_2$ -receptors mainly located in the bronchi and peripheral vessels. BETALOC (metoprolol tartrate) 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. 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, BETALOC (metoprolol tartrate) has less effect on the peripheral circulation and the bronchial muscles than non selective beta-blockers. However, BETALOC (metoprolol tartrate) 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 beta-2 stimulants may require adjustment of the dosage of these if metoprolol tartrate 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. BETALOC (metoprolol tartrate) will inhibit catecholamine-induced lipolysis.

BETALOC (metoprolol tartrate) has also been shown to reduce diuretic induced increase in plasma renin activity. BETALOC (metoprolol tartrate) will inhibit catecholamine induced insulin secretion to a far lesser degree than non-selective beta-blockers.

BETALOC (metoprolol tartrate) 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.

BETALOC (metoprolol tartrate) forms an active metabolite (2-hydroxymetoprolol), which does not, however, contribute significantly to the therapeutic effect.

BETALOC (metoprolol tartrate) 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**

BETALOC (metoprolol tartrate) 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% of BETALOC (metoprolol tartrate) is bound to human serum proteins.

### **Metabolism and Excretion**

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 tartrate has a linear relationship to its plasma concentration. BETALOC (metoprolol tartrate) is excreted mainly by glomerular filtration

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

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

### **Dose-response**

The duration of the beta-blocking effect is dose dependent (as measured by reduction of exercise heart rate). For instance, in healthy subjects the effect of 20 mg metoprolol tartrate 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 subjects, in a study involving eight healthy elderly (mean age 74.5 years) and eight healthy young (mean age 26.3 years) subjects.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

No data available.

### **Carcinogenicity**

No data available.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

See Section 2 Qualitative and quantitative composition.

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See Section 4.5 Interactions with other medicines and other forms of interactions for information regarding interactions.

### **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**

BETALOC tablets: Store below 30°C. Protect from moisture.

BETALOC injection: Store below 25°C. Protect from light.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

#### **Tablets 50 mg**

Available in blister packs of 100 tablets.

#### **Tablets 100 mg**

Available in blister packs of 60 tablets.

#### **Injection solution, 1mg/mL**

Available in glass ampoules of 5 mL, in packs of 5.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

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

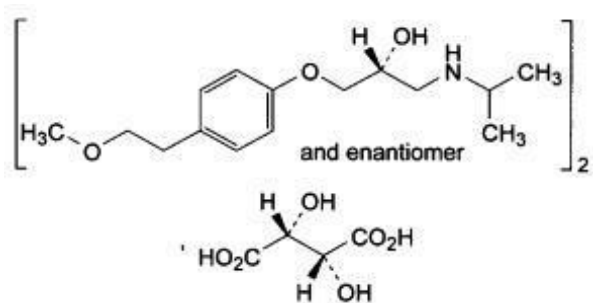
### **6.7 PHYSICOCHEMICAL PROPERTIES**

Metoprolol tartrate, di(±)-1-(isopropylamine)-3-[*p*-(2-methoxyethyl) phenoxy] -2 propranol *L* (+)-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 beta-blockers.

#### **Chemical structure**

The molecular formula is (C<sub>15</sub>H<sub>25</sub>NO<sub>3</sub>)<sub>2</sub>.C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>



**Figure 1** Chemical structure of metoprolol tartrate

**CAS number**

56392-17-7

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

Prescription only medicine (Schedule 4)

**8 SPONSOR**

AstraZeneca Pty Ltd  
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**9 DATE OF FIRST APPROVAL**

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**10 DATE OF REVISION**

23 October 2019

**SUMMARY TABLE OF CHANGES**

Section changed	Summary of new information
All	PI reformat
4.6	Maternofetal monitoring added for use in pregnancy

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