

NEW ZEALAND DATA SHEET**NAME OF MEDICINE**

BETALOC IV
metoprolol tartrate 1 mg/mL injection

PRESENTATION

Ampoule – a clear, colourless liquid free from foreign particles containing 5 mL of 1 mg/mL metoprolol tartrate.

USES**ACTIONS**

Metoprolol is a beta₁-selective beta-blocker, ie. it blocks beta₁-receptors at doses much lower than those needed to block beta₂-receptors.

Metoprolol has an insignificant membrane-stabilising effect and does not display partial agonist activity.

Metoprolol reduces or inhibits the agonistic effect on the heart of catecholamines (which are released during physical and mental stress). This means that the usual increase in heart rate, cardiac output, cardiac contractility and blood pressure, produced by the acute increase in catecholamines, is reduced by metoprolol.

During high endogenous adrenaline levels metoprolol interferes much less with blood pressure control than non-selective beta-blockers.

When mandatory, metoprolol, in combination with a beta₂-agonist, may be given to patients with symptoms of obstructive pulmonary disease. When given together with a beta₂-agonist, metoprolol in therapeutic doses interferes less than non-selective beta-blockers with the beta₂-mediated bronchodilation caused by the beta₂-agonist.

Metoprolol interferes less with insulin release and carbohydrate metabolism than do non-selective beta-blockers.

Metoprolol interferes much less with the cardiovascular response to hypoglycaemia than do non-selective beta-blockers.

Short term studies have shown that metoprolol may cause a slight increase in triglycerides and a decrease in free fatty acids in the blood. In some cases, a small decrease in the high density lipoproteins (HDL) fraction has been observed, although to a lesser extent than that following non-selective beta-blockers. However, a significant reduction in total serum cholesterol levels has been demonstrated after metoprolol treatment in one study conducted over several years.

Quality of life is maintained uncompromised, or improved during treatment with metoprolol. An improvement in quality of life has been observed after metoprolol treatment in patients after myocardial infarction.

In men with mild to moderate hypertension metoprolol has been shown to reduce the risk of death from cardiovascular disease, mainly due to a reduced risk for sudden cardiovascular death, to reduce the risk for fatal and non-fatal myocardial infarction and for stroke.

Effect on Cardiac Rhythm

Metoprolol is suitable for regulating the heart rate in cases of supraventricular tachycardia or atrial fibrillation, and in the presence of ventricular extrasystoles.

Effect on Myocardial Infarction

Metoprolol reduces mortality in patients with suspected or confirmed myocardial infarction mainly due to a reduction in the risk of sudden death. This effect is presumed to partly be due to the prevention of ventricular fibrillation. The anti-fibrillatory effect is believed to be due to a dual mechanism: a vagal effect within the blood-brain barrier beneficially influencing electrical stability of the heart, and a sympathetic direct cardiac anti-ischaemic effect beneficially influencing contractility, heart rate and blood pressure. For both early and late intervention the reduction in mortality is also present in high risk patients with previous cardiovascular disease; and in patients with diabetes mellitus.

Metoprolol has also been shown to reduce the risk for non-fatal myocardial infarction.

These anti-ischaemic effects of metoprolol are also reflected in a reduction in chest pain during the acute infarction phase. Metoprolol has also been shown to reduce the incidence of recurrent myocardial infarction.

PHARMACOKINETICS

Absorption and Distribution

Metoprolol is rapidly distributed during 5-10 minutes after IV injection. The plasma levels show a linear relationship with the dose administered in the dose range 5-20 mg. The plasma protein binding of metoprolol is low, approximately 5-10%.

Metabolism and elimination

Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. Three main metabolites of metoprolol have been identified, though none of them have a beta-blocking effect of clinical importance.

As a rule over 95% of an oral dose can be recovered in the urine. About 5% of the given dose is excreted in the urine in unchanged form, this figure rising up to 30% in isolated cases. The elimination half-life of metoprolol in plasma averages 3.5 hours (extremes: 1 and 9 hours). The total clearance rate is approximately 1 litre/minute.

The elderly show no significant changes in the pharmacokinetics of metoprolol as compared to young persons. The systemic bioavailability and elimination of metoprolol is unchanged in patients with reduced renal function, however the excretion of metabolites is reduced. Significant accumulation of metabolites was observed in patients with a glomerular filtration rate (GFR) of less than 5 mL/minute. This accumulation of metabolites does not increase the beta-blockade.

The pharmacokinetics of metoprolol is little affected by decreased liver function due to its low protein binding. However, in patients with severe liver cirrhosis and a portacaval shunt the bioavailability may increase and the total clearance may be reduced. Patients with a portacaval anastomosis had a total clearance of approximately 0.3 L/min and area under the plasma concentration-time curve (AUC) values of up to 6 times higher than in healthy subjects.

INDICATIONS

- Cardiac arrhythmias, especially supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and ventricular extrasystoles.
- Suspected or definite myocardial infarction.

DOSAGE AND ADMINISTRATION**CARDIAC ARRHYTHMIAS**

Initially up to 5 mg injected intravenously at a rate of 1-2 mg per minute. The injection can be repeated at 5-minute intervals until a satisfactory effect is achieved. A total dose of 10-15 mg generally proves sufficient. Doses of 20 mg or more are unlikely to result in further therapeutic benefit.

MYOCARDIAL INFARCTION

Metoprolol should be administered intravenously as soon as possible after symptoms indicating acute myocardial infarction.

Such treatment should be initiated in a coronary care or similar unit immediately after the patient's haemodynamic condition has stabilised. Three 5 mg bolus injections should be given at 2 minute intervals depending on the haemodynamic status of the patient (ECG, blood pressure, heart rate). See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS.

In patients who tolerate the full intravenous dose (15 mg), BETALOC CR tablets 47.5 mg four times daily should be started 15 minutes after the last intravenous injection and be continued for 24 hours, followed by BETALOC CR tablets 95 mg twice daily for the next 24 hours

The maintenance dose is BETALOC CR 190 mg once daily.

Patients who do not tolerate the full intravenous (15 mg) dose of metoprolol should have their oral treatment initiated with caution starting with a lower dose.

IMPAIRED RENAL FUNCTION

Dose adjustment is not needed in patients with impaired renal function

IMPAIRED HEPATIC FUNCTION

Dose adjustment is not normally needed in patients suffering from liver cirrhosis because metoprolol has low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g. shunt-operated patients) a reduction in dose should be considered.

ELDERLY

Dose adjustment is not needed.

CHILDREN

There is limited experience with metoprolol treatment in children.

CONTRAINDICATIONS

- Bronchial asthma or other obstructive lung disorders.
- Grade 2 and 3 A-V block and intranodal A-V block.
- Patients with unstable decompensated cardiac heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism.

- Marked clinically relevant bradycardia.
- Sick-sinus syndrome.
- Cardiogenic shock.
- Severe peripheral arterial circulatory disorder.

Metoprolol should not be given to patients with suspected acute myocardial infarction as long as the heart rate is <45 beats/minute, the P-Q interval is > 0.24 seconds or the systolic blood pressure is <100 mmHg.

BETALOC is contraindicated in patients who have shown hypersensitivity to metoprolol tartrate or to other beta-blockers.

WARNINGS AND PRECAUTIONS

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with beta-blockers.

During treatment with metoprolol, the risk of interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.

Patients suffering from heart failure should have their decompensation treated both before and during treatment with metoprolol.

Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block) by beta-blockade.

If the patients develop increasing bradycardia, metoprolol should be given in lower doses or gradually withdrawn.

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Where metoprolol is prescribed for a patient known to be suffering from phaeochromocytoma, an alpha-blocker should be given concomitantly.

During oral treatment abrupt interruption of the medication is to be avoided. If treatment has to be withdrawn it should, when possible, be done gradually over a period of at least 10-14 days in diminishing doses to 23.75 mg daily for the last 6 days. During this period especially patients with known ischaemic heart disease should be kept under close observation. The risk for coronary events, including sudden death, may increase during the withdrawal of beta-blockade.

Prior to surgery, the anaesthetist should be informed that the patient is receiving metoprolol. It is not recommended to stop beta-blocker treatment in patients undergoing surgery. 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.

In patients taking beta-blockers anaphylactic shock assumes a more severe form.

In cases where the systolic blood pressure is below 100 mmHg metoprolol should only be given intravenously if special precautions are observed, because there is a risk that

administration of the medicine by this route may cause a further fall in blood pressure, (i.e. in patient's with cardiac arrhythmias).

When treating patients with suspected or definite myocardial infarction the haemodynamic status of the patient should be carefully monitored after each of the three 5 mg intravenous doses.

The second or third dose should not be given if the heart rate is <40 beats/minute, the P-Q interval is > 0.26 seconds and the systolic blood pressure is <90 mmHg or if there is any aggravation of dyspnoea or cold sweating.

USE IN PREGNANCY

As with most medicines, metoprolol should not be given during pregnancy and lactation unless its use is considered essential. As with all antihypertensive agents, beta-blockers may cause side effects (e.g. bradycardia) in the foetus and in the newborn and breast-fed infant.

USE IN LACTATION

The amount of metoprolol ingested via breast-milk seems to be negligible as regards beta-blocking effect in the infant if the mother is treated with metoprolol doses within the normal therapeutic range.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should know how they react to metoprolol before they drive or use machines because occasionally dizziness or fatigue may occur.

ADVERSE EFFECTS

BETALOC is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use..

The following definitions of frequencies are used: Very common ($\geq 10\%$), common (1-9.9%), uncommon (0.1–0.9%), rare (0.01–0.09%) and very rare (<0.01%).

CARDIOVASCULAR SYSTEM

Common: Bradycardia, postural disorders (very rarely with syncope), cold hands and feet, palpitations.

Uncommon: Deterioration of heart failure symptoms, cardiogenic shock in patients with acute myocardial infarction*, first degree heart block, oedema, pericardial pain.

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 46,000 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 patient in which metoprolol is recommended for use in acute myocardial infarction.

CENTRAL NERVOUS SYSTEM

Very common: Fatigue

Common: Dizziness, headache.

Uncommon: Paraesthesiae, muscle cramps.

GASTROINTESTINAL

Common: Nausea, abdominal pain, diarrhoea, constipation.

Uncommon: Vomiting

Rare: Dry mouth

HAEMATOLOGIC

Very rare: Thrombocytopenia

HEPATIC

Rare: Liver function test abnormalities

Very rare: Hepatitis

METABOLISM

Uncommon: Weight gain

MUSCULOSKELETAL

Very rare: Arthralgia

PSYCHIATRIC

Uncommon: Depression, concentration impaired, somnolence or insomnia, nightmares

Rare: Nervousness, anxiety, impotence / sexual dysfunction.

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

RESPIRATORY

Common: Dyspnoea on exertion.

Uncommon: Bronchospasm

Rare: Rhinitis

SENSE ORGANS

Rare: Disturbances of vision, dry and/or irritated eyes, conjunctivitis

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.

INTERACTIONS

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Drugs that act as enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. Plasma levels of metoprolol may be raised by co-administration of compounds metabolised by CYP2D6 eg. antiarrhythmics, antihistamines, histamine-2-receptor antagonists, antidepressants, antipsychotics and COX-2 inhibitors. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

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

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

Increased negative inotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists of the verapamil and diltiazem type. In patients treated with beta-blockers, intravenous administration of calcium antagonists of the verapamil type should not be given.

Beta-blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents (of the quinidine type and amiodarone).

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

In patients receiving beta-blocker therapy, inhalation anaesthetics enhance the cardiodepressant effect.

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

Under certain conditions, when adrenaline is administered to patients treated with beta-blockers, cardioselective beta-blockers interfere much less with blood pressure control than non-selective beta-blockers.

The dosages of oral antidiabetics may have to be readjusted in patients receiving beta-blockers.

OVERDOSAGE

The symptoms of overdose may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include:

Close supervision, treatment in an intensive care ward and the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given.

Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Administration of calcium ions may also be considered. Bronchospasm can usually be reversed by bronchodilators.

PHARMACEUTICAL PRECAUTIONS

SHELF-LIFE

Shelf-life: Ampoules 1 mg/mL: 5 years

Diluted metoprolol tartrate injection 1 mg/mL should be used within 12 hours.

SPECIAL PRECAUTIONS FOR STORAGE

BETALOC IV should be stored at or below 25°C.

COMPATIBILITIES

Metoprolol tartrate injection 1 mg/mL corresponding to 40 mg metoprolol can be added to 1000 mL of the following infusion solutions:

Sodium chloride 0.9%, Mannitol 150 mg/mL, Dextrose 100 mg/mL, Dextrose 50 mg/mL, Fructose 200 mg/mL, Invert sugar 100 mg/mL, Ringer's injection, Ringer-dextrose and Acetated Ringer's.

INCOMPATIBILITIES

Metoprolol tartrate solution for injection 1 mg/mL should not be added to Macrodex.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

Ampoules 5 mL, 1 mg/mL – pack of 5 x 5 mL

FURTHER INFORMATION**LIST OF EXCIPIENTS**

Sodium chloride for injection and water for injection.

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DATE OF PREPARATION

5 April 2011

CDS 0309

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