Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betaloc 1 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 1 mg metoprolol tartrate.
Each ampoule of 5 ml contains 5 mg metoprolol tartrate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection. (Injection)
Clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Control of tachyarrhythmias, especially supraventricular tachyarrhythmias. The electrocardiogram should be monitored while undergoing treatment.
Early intervention with Betaloc Injection in acute myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics. Betaloc Injection has been shown to reduce mortality when administered to patients with acute myocardial infarction.

4.2 Posology and method of administration

Posology
The dose must always be adjusted to the individual requirements of the patient. The following are guidelines:
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 response has been obtained. A total dose of 10–15 mg generally proves sufficient.
Because of the risk of a pronounced drop of blood pressure, the i.v. administration of Betaloc to patients with a systolic blood pressure below 100 mmHg should only be given with special care.
During anaesthesia: 2-4 mg injected slowly i.v. at induction is usually sufficient to prevent the development of arrhythmias during anaesthesia. The same dosage can also be used to control arrhythmias developing during anaesthesia. Further injections of 2 mg may be given as required to a maximum overall dose of 10 mg.
Myocardial infarction: Early intervention. To achieve optimal benefits from intravenous Betaloc, suitable patients should present within 12 hours of the onset of chest pain.
Intravenous Betaloc Injection should be initiated in a coronary care or similar unit when the patient's haemodynamic condition has stabilised.
Therapy should commence with 5 mg i.v. every 2 minutes to a maximum of 15 mg total as determined by blood pressure and heart rate. The second or third dose should not be given if the systolic blood pressure is <90 mmHg, the heart rate is <40 beats/min and the P-Q time is >0.26 seconds, or if there is any aggravation of dyspnoea or cold sweating.
Oral therapy should commence 15 minutes after the last injection with 50 mg every 6 hours for 48 hours. Patients who fail to tolerate the full intravenous dose should be given half the suggested oral dose.
Renal impairment:Dose adjustment is generally not needed in patients with impaired renal function.
Hepatic impairment: Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has a low protein binding
(5–10%). However, in patients with severe hepatic dysfunction a reduction in dosage may be necessary.
Elderly: Several studies indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol. Dose adjustment is not needed in the elderly, but careful dose titration is important in all patients.
Paediatric population: The safety and efficacy of metoprolol in children has not been established.

4.3 Contraindications

Betaloc Injection, as with other beta-blockers, should not be used in patients with any of the following:

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
- Hypotension
- AV block of second- or third-degree.
- Unstable decompensated cardiac failure (pulmonary oedema, hypoperfusion or hypotension).
- Continuous or intermittent inotropic therapy acting through beta-receptor agonism.
- Bradycardia (<45 bpm).
- Sick sinus syndrome (unless a permanent pacemaker is in place).
- Cardiogenic shock.
- Severe peripheral arterial circulatory disorders.
- Untreated phaeochromocytoma.
- Metabolic acidosis.Known hypersensitivity to any component of Betaloc Injection or other beta-blockers.

Betaloc Injection is also contraindicated when suspected acute myocardial infarction is complicated by bradycardia (<45 bpm), first-degree heart block (the P-Q interval is >0.24 sec) or systolic blood pressure <100 mmHg and/or severe heart failure.

4.4 Special warnings and precautions for use

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/min, the systolic blood pressure is <90 mmHg and the P-Q time is >0.26 sec, or if there is any aggravation of dyspnoea or cold sweating.
Betaloc injection, as with other beta blockers:

- should not be withdrawn abruptly during oral treatment. When possible, Betaloc i.v. should be withdrawn gradually over a period of 10 – 14 days, in diminishing doses to 25 mg daily for the last 6 days. During its withdrawal patients should be kept under close surveillance, especially those with known ischaemic heart disease. The risk for coronary events, including sudden death, may increase during the withdrawal of beta-blockade.
- must be reported to the anaesthetist prior to general anaesthesia. It is not generally recommended to stop Betaloc i.v. treatment in patients undergoing surgery. If withdrawal of metoprolol is considered desirable, this should, if possible, be completed at least 48 hours before general anaesthesia. Routine initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension, stroke and increased mortality in patients with cardiovascular risk factors. However in some patients it may be desirable to employ a beta-blocker as premedication. In such cases an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression.
- although contra-indicated in severe peripheral arterial circulatory disturbances (see Section 4.3), may also aggravate less severe peripheral arterial circulatory disorders.
- may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure, or patients known to have a poor cardiac reserve. Betaloc i.v. should be used with caution in patients where cardiac reserve is poor. •may cause patients to develop increasing bradycardia, in such cases the Betaloc i.v. dosage should be reduced or gradually withdrawn.
- due to the negative effect on conduction time, should only be given with caution to patients with first-degree heart block.
- may increase the number and duration of angina attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Betaloc i.v. is a $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- may mask the early signs of acute hypoglycaemia, in particular tachycardia. During treatment with Betaloc i.v., the risk of interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.
- may mask the symptoms of thyrotoxicosis.

- may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Although cardioselective beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. When administration is necessary, these patients should be kept under close surveillance. The use of a $beta_2$-bronchodilator (e.g. terbutaline) may be advisable in some patients. The dosage of the $beta_2$-agonist may require an increase when treatment with Betaloc i.v. is commenced.

The label shall state - "Use with caution in patients who have a history of wheezing, asthma or any other breathing difficulties, see enclosed user leaflet."

Like all beta-blockers, careful consideration should be given to patients with psoriasis before Betaloc i.v. is administered.

In patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy.

Intravenous administration of calcium antagonists of the verapamil type should not be given to patients treated with beta-blockers.
The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.
This medicinal product contains less than 1 mmol sodium (23mg) per ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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. Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of Betaloc i.v. whereas enzyme inhibitors (e.g. cimetidine, alcohol and hydralazine) may increase plasma concentrations. Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other beta blockers (i.e. eye drops), or Mono Amine Oxidase (MAO) inhibitors should be kept under close surveillance.
If concomitant treatment with clonidine is to be discontinued, Betaloc i.v. 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 indometacin and other prostaglandin synthetase inhibiting drugs may reduce the antihypertensive effect of beta-blockers.
The administration of adrenaline (epinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with $beta_1$-selective drugs.
Betaloc i.v. will antagonise the $beta_1$-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of $beta_2$-agonists at normal therapeutic doses.
Metoprolol may impair the elimination of lidocaine.
As with other beta-blockers, concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.
The dosages of oral antidiabetic agents and also of insulin may have to be readjusted in patients receiving beta-blockers.
As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently.
The effects of Betaloc i.v. and other drugs with an antihypertensive effect on blood pressure are usually additive. Care should be taken when combining with other antihypertensive drugs or drugs that might reduce blood pressure such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

Betaloc Injection should not be used in pregnancy or nursing mothers unless the physician considers that the benefit outweighs the possible hazard to the foetus/infant. 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 maternofoetal monitoring be performed in pregnant women treated with Betaloc Injection.
As with all beta-blockers, Betaloc Injection may cause side effects especially bradycardia and hypoglycaemia in the foetus, and in the newborn and breast-fed infant. There is an increased risk of cardiac and pulmonary complications in the neonate.
Betaloc Injection has, however, been used in pregnancy-associated hypertension under close supervision, after 20 weeks gestation. Although Betaloc Injection crosses the placental barrier and is present in the cord blood, as yet no evidence of foetal abnormalities has been reported.
Breast-feeding
Breast-feeding is not recommended. The amount of metoprolol ingested via breast milk should not produce significant beta-blocking effects in the neonate if the mother is treated with normal therapeutic doses.

4.7 Effects on ability to drive and use machines

Betaloc Injection has a minor influence on the ability to drive and use machines. It should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Metoprolol 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 (≥1/10), common (≥1/100 to <1/10), uncommon ((≥1/1,000 to <1/100), rare ((≥1/10,000 to <1/1,000) and very rare (<1/10,000).

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Very rare	Gangrene in patients with pre existing severe peripheral circulatory disorders
Blood and lymphatic system disorders	Very rare	Thrombocytopenia
Psychiatric disorders	Uncommon	Depression, insomnia, nightmares
	Rare	Nervousness, anxiety
	Very rare	Confusion, hallucinations
Nervous system disorders	Common	Dizziness, headache
	Uncommon	Concentration impairment, somnolence, paraesthesiae
	Very rare	Amnesia/memory impairment, taste disturbances
Eye disorders	Rare	Disturbances of vision, dry and/or irritated eyes, conjunctivitis
Ear and labyrinth disorders	Very rare	Tinnitus
Cardiac disorders	Common	Bradycardia, palpitations
	Uncommon	Deterioration of heart failure symptoms, cardiogenic shock in patients with acute myocardial infarction*, first-degree heart block
	Rare	Disturbances of cardiac conduction, cardiac arrhythmias, increased existing AV block
Vascular disorders	Common	Postural disorders (very rarely with syncope)
	Rare	Raynauds phenomenon
	Very rare	Increase of pre-existing intermittent claudication
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea on exertion
	Uncommon	Bronchospasm
	Rare	Rhinitis
Gastrointestinal disorders	Common	Nausea, abdominal pain, diarrhoea, constipation
	Uncommon	Vomiting
	Rare	Dry mouth
Hepatobiliary disorders	Very rare	Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Rash (in the form of psoriasiform urticaria and dystrophic skin lesions), increased sweating
	Rare	Loss of hair
	Very rare	Photosensitivity reactions, aggravated psoriasis

Musculoskeletal and connective tissue disorders	Very rare	Arthralgia
	Uncommon	Muscle cramps
Reproductive system and breast disorders	Rare	Impotence/sexual dysfunction
General disorders and administration site disorders	Very common	Fatigue
	Common	Cold hands and feet
	Uncommon	Precordial pain, oedema
Investigations	Uncommon	Weight gain
	Rare	Liver function test abnormalities, positive anti-nuclear antibodies (not associated with SLE)

*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 corresponding excess frequency for patients in Killip class I was 0.7% (metoprolol 3.5% and placebo 2.8%). 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms

Symptoms of overdose may include hypotension, cardiac insufficiency, bradycardia and bradyarrhythmia, cardiac conduction disturbances and bronchospasm.

Management

Care should be provided at a facility that can provide appropriate supporting measures, monitoring, and supervision.
Atropine, adrenostimulating 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 adrenostimulating drugs such as dobutamine, with α_1 receptor agonistic drugs added in presence of vasodilation. Intravenous use of Ca^{2+} can also be considered.
Bronchospasm can usually be reversed by bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07AB02

Mechanism of action

Metoprolol is a competitive beta-adrenoceptor antagonist. It acts preferentially to inhibit beta-adrenoceptors (conferring some cardioselectivity), is devoid of intrinsic sympathomimetic activity (partial agonist activity) and possesses beta-adrenoceptor blocking activity comparable in potency with propranolol.

Pharmacodynamic effects

A negative chronotrophic effect on the heart is a consistent feature of metoprolol administration. Thus, cardiac output and systolic blood pressure rapidly decrease following acute administration.

Clinical efficacy and safety

The intention to treat trial COMMIT included 45,852 patients admitted to hospital within 24 hours of the onset of symptoms of suspected acute myocardial infarction with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients were randomly allocated to metoprolol (up to 15 mg intravenous then 200 mg oral) or placebo and treated until discharge or up to 4 weeks in hospital. The two co-primary outcomes were: (1) composite of death, reinfarction or cardiac arrest; and (2) death from any cause during the scheduled treatment period. Neither of the co-primary outcomes was significantly reduced by metoprolol. However, metoprolol treatment was associated with fewer people having reinfarction and ventricular fibrillation but an increased rate of cardiogenic shock during the first day after admission. There was substantial net

hazard in haemodynamically unstable patients. There was moderate net benefit in those who were stable, particularly after days 0-1.

5.2 Pharmacokinetic properties

Absorption
Absorption is complete after intravenous administration.
Distribution
The plasma protein binding of metoprolol is low, approximately 5-10%. Metoprolol crosses the blood brain barrier and placenta, maternal and foetal concentrations are equal.
Biotransformation
Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme.
Elimination
Metoprolol is eliminated mainly by hepatic metabolism. Plasma half-life is 3.5 hours (range 1-9 hours). Rates of metabolism vary between individuals, with poor metabolisers (approximately 10%) showing higher plasma concentrations and slower elimination than extensive metabolisers. Within individuals, however, plasma concentrations are stable and reproducible.
As a rule, over 95% of an oral dose can be recovered in the urine. About 5% of the given oral dose and 10% of an i.v. dose is excreted in the urine in unchanged form, this figure rising up to 30% in isolated cases.
Linearity/non-linearity
Plasma levels rise linearly in relation to dose.

5.3 Preclinical safety data

Pre-clinical information has not been included because the safety profile of metoprolol tartrate has been established after many years of clinical use. Please refer to section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened pack: 5 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton in order to protectfrom light.

6.5 Nature and contents of container

Type I, 5 ml glass ampoule. Carton of five ampoules.

6.6 Special precautions for disposal and other handling

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Recordati Ireland Limited

Raheens East
Ringaskiddy
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1404/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 2nd May 2008

10 DATE OF REVISION OF THE TEXT

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