

## NEW ZEALAND DATA SHEET

### 1. NAME OF MEDICINE

BETALOC<sup>®</sup> CR 23.75 mg Modified release tablet  
BETALOC<sup>®</sup> CR 47.5 mg Modified release tablet  
BETALOC<sup>®</sup> CR 95 mg Modified release tablet  
BETALOC<sup>®</sup> CR 190 mg Modified release tablet

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains metoprolol succinate 23.75 mg, 47.5 mg, 95 mg or 190 mg.

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Modified release tablets of metoprolol succinate, (will be referred to as controlled release tablets in the following text).

CR tablets 23.75 mg – A controlled-release preparation in which the active substance metoprolol succinate, is embedded as coated beads in a disintegrating tablet. A white to off-white, oval, biconvex, film-coated tablet scored on both sides and engraved A/β on one side. Size: 5.5 x 10.5 mm. The tablet can be divided into equal doses. Average mass 0.17g. Each tablet contains 23.75 mg metoprolol succinate, bioequivalent to 25 mg metoprolol tartrate.

CR tablets 47.5 mg - A controlled-release preparation in which the active substance metoprolol succinate is embedded as coated beads in a disintegrating tablet. A white to off-white, circular, biconvex, film-coated tablet with a score on one side and engraving A/mO on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Diameter 9 mm. Average mass 0.22 g. Each tablet contains 47.5 mg metoprolol succinate, bioequivalent to 50 mg metoprolol tartrate.

CR tablets 95 mg - A controlled-release preparation in which the active substance metoprolol succinate is embedded as coated beads in a disintegrating tablet. A white to off-white, circular, biconvex, film-coated tablet with a score on one side and engraving A/mS on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Diameter 10 mm. Average mass 0.37 g. Each tablet contains 95 mg metoprolol succinate, bioequivalent to 100 mg metoprolol tartrate.

CR tablets 190 mg - A controlled-release preparation in which the active substance metoprolol succinate is embedded as coated beads in a disintegrating tablet. A white to off-white, oval, biconvex, film-coated tablet with a score on one side and engraving A/mY on the same side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Size 8.5 mm x 17 mm. Average mass 0.71 g. Each tablet contains 190 mg metoprolol succinate, bioequivalent to 200 mg metoprolol tartrate.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

- Hypertension. To reduce blood pressure and to reduce the risk of cardiovascular and coronary mortality (including sudden death), and morbidity.
- Angina pectoris.
- Symptomatic mild to severe chronic heart failure as an adjunct to other heart failure therapy to: increase survival, reduce hospitalisation, improve left ventricular function, improve New York Heart Association (NYHA) functional class and improve Quality of Life.
- Cardiac arrhythmias, especially supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and ventricular extrasystoles.
- Maintenance treatment after myocardial infarction
- Hyperthyroidism.
- Functional heart disorder with palpitations.
- Migraine prophylaxis.
- Paediatric hypertension

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage should always be adjusted to the patient's individual requirements.

BETALOC CR is intended for once-daily treatment and can be taken with or without food. The BETALOC CR tablets should be swallowed with liquid. The tablets and the divided halves should not be chewed or crushed.

The following dosage recommendations may be taken as a guide:

#### **Hypertension**

The recommended dose in patients with mild to moderate hypertension is 47.5 mg BETALOC CR given once daily. In patients not responding to 47.5 mg the dose can be increased to 95-190 mg once daily or combined with other antihypertensive agents.

Long-term antihypertensive treatment with metoprolol in daily doses of 95-190 mg has been shown to reduce total mortality, including sudden cardiovascular death, stroke and coronary events in hypertensive patients.

#### **Angina Pectoris**

95-190 mg daily given as a single dose in the morning. BETALOC CR can be combined with other antianginal agents if needed.

#### **Chronic heart failure**

The dose of BETALOC CR should be individually adjusted in patients with chronic heart failure stabilised on other heart failure treatment. A recommended initial dose during the first two weeks is a 23.75 mg tablet once daily. It is recommended that patients with NYHA functional classes III-IV begin with half a 23.75 mg tablet once daily for the first week. It is recommended that the dose then be doubled every second week up to a maximum target dose of 190 mg BETALOC CR once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 190 mg BETALOC CR once daily (or the highest tolerated dose).

At each dose level the patient should be carefully evaluated with regard to tolerability. In the

case of hypotension, a decrease in concomitant medication may be necessary. Initial hypotension does not necessarily mean that the dose cannot be tolerated in chronic treatment but the patient should be kept at the lower dose until stabilised.

### **Cardiac Arrhythmias**

95-190 mg daily, given as a single dose once daily.

### **Maintenance treatment after myocardial infarction**

Long-term oral treatment with metoprolol in doses of 190 mg given once daily has been shown to reduce the risk of death (including sudden death) and to reduce the risk of reinfarction (also in patients with diabetes mellitus).

### **Functional Heart Disorder With Palpitations**

The recommended dosage is 95 mg once daily. If necessary, the dose may be increased to 190 mg.

### **Migraine Prophylaxis**

The recommended dosage is 95-190 mg once daily.

### **Hyperthyroidism**

95-190 mg daily, given as a single dose in the morning. If necessary, the dose may be increased.

### **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.

### **Hypertension in Children**

The recommended initial dosage in hypertensive patients  $\geq 6$  years is 0.95 mg/kg BETALOC CR, not exceeding 47.5 mg once daily given approximated by dose strength. In patients not responding to 0.95 mg/kg, the dose can be increased to a maximum daily dose of 1.90 mg/kg. Doses above 190 mg once daily have not been studied in children and adolescents.

Efficacy and safety of use in children  $< 6$  years have not been studied.

## **4.3 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 failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism.

- Marked clinically relevant sinus bradycardia.
- Sick-sinus syndrome (unless a permanent pacemaker is in place).
- 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 CR is contraindicated in patients who have shown hypersensitivity to any component of the product or to other beta-blockers.

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

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

The risk of BETALOC CR interfering with beta<sub>2</sub>-receptors is less than with conventional tablet formulations of beta<sub>1</sub>-selective blockers.

The risk of interfering with carbohydrate metabolism or masking hypoglycaemia is likely to be less with BETALOC CR than with conventional tablet formulations of beta<sub>1</sub>-selective blockers and much less than with non-selective beta-blockers.

Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). If the patient develops increasing bradycardia, BETALOC CR should be given in lower doses or gradually withdrawn.

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

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

Abrupt withdrawal of beta-blockade is hazardous especially in high risk patients, and therefore should not be done. If there is a need to discontinue treatment with BETALOC CR, this should preferably be done gradually over at least two weeks when the dose is reduced by half in each step down to the final step when a whole 23.75 mg tablet is reduced to half a tablet. If symptoms occur, a slower withdrawal rate is recommended. Sudden withdrawal of beta-blockade may aggravate chronic heart failure and also increases the risk for myocardial infarction and sudden death.

The anaesthetist should be informed that the patient is receiving BETALOC CR prior to surgery. 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.

## 4.5 INTERACTION WITH OTHER MEDICINES 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. Plasma levels of metoprolol may be raised by co-administration of compounds metabolised by CYP2D6 e.g. 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.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Pregnancy

As with most medicines, BETALOC CR should not be given during pregnancy and lactation 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. 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.

## Breast-feeding

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.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 4.8 UNDESIRABLE EFFECTS

BETALOC CR 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, mostly with conventional metoprolol (metoprolol tartrate). In many cases a relationship to treatment with metoprolol has not been established. 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, precordial 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

**4.9 OVERDOSE****Symptoms**

Symptoms of overdosage 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.

If justified, gastric lavage and/or activated charcoal can be administered.

Atropine, adreno-stimulating medicines 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 medicines such as dobutamine with  $\alpha_1$ -receptor agonistic medicines added in presence of vasodilation. Intravenous use of calcium ions can also be considered.

Bronchospasm can usually be reversed by bronchodilators.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.2 PHARMACODYNAMIC PROPERTIES

Metoprolol is a beta<sub>1</sub>-selective beta-blocker, i.e. it blocks beta<sub>1</sub> –receptors at doses much lower than those needed to block beta<sub>2</sub>-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.

BETALOC CR gives an even plasma concentration time and effect profile (beta<sub>1</sub>-blockade) over 24 hours in contrast to conventional tablet formulations of beta<sub>1</sub>-selective blockers.

Due to the lack of pronounced peaks in plasma concentration, the clinical beta<sub>1</sub>-selectivity is improved with the BETALOC CR formulation when compared to the conventional tablet formulations of beta<sub>1</sub>-selective blockers. Furthermore the potential risk for peak plasma concentration related side-effects, such as bradycardia and leg fatigue is reduced.

When mandatory, BETALOC CR, in combination with a beta<sub>2</sub>-agonist, may be given to patients with symptoms of obstructive pulmonary disease. When given together with a beta<sub>2</sub>-agonist, BETALOC CR in therapeutic doses interferes less than non-selective beta-blockers with the beta<sub>2</sub>-mediated bronchodilation caused by the beta<sub>2</sub>-agonist.

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

BETALOC CR interferes much less with the cardiovascular response to hypoglycaemia than



do non-selective beta-blockers.

Short term studies have shown that BETALOC CR 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 BETALOC CR. An improvement in quality of life has been observed after metoprolol treatment in patients after myocardial infarction. Furthermore, BETALOC CR has been shown to improve Quality of Life in patients with chronic heart failure.

## **CLINICAL EFFICACY AND SAFETY**

### **Effect in hypertension**

BETALOC CR lowers elevated blood pressure both in the standing and supine position. A short duration (a few hours) and clinically insignificant increase in peripheral resistance may be observed after the institution of metoprolol treatment. During long-term treatment total peripheral resistance may be reduced, due to reversal of hypertrophy in arterial resistance vessels. Long-term antihypertensive therapy with metoprolol has also been shown to reduce left ventricular hypertrophy and to improve left ventricular diastolic function and left ventricular filling.

In 144 paediatric patients (6 to 16 years of age) with essential hypertension, BETALOC CR has been shown in a 4-week study to reduce placebo-corrected systolic blood pressure for the 0.95 and 1.90 mg/kg doses (4 to 6 mmHg). For diastolic blood pressure, there was a placebo-corrected reduction for the 1.90 mg/kg dose (5 mmHg) and a dose-dependent reduction for the dose range 0.19, 0.95 and 1.90 mg/kg. No apparent differences in blood pressure reduction were observed based on age, Tanner stage or race.

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 infarction and for stroke.

### **Effect on angina pectoris**

In patients with angina pectoris metoprolol has been shown to reduce the frequency, duration and severity of both angina attacks and silent ischaemic episodes and to increase the physical working capacity.

### **Effect in chronic heart failure**

In patients with symptoms of heart failure (New York Heart Association (NYHA) II-IV) and decreased ejection fraction ( $\leq 0.40$ ) BETALOC CR when added to standard therapy has been shown to improve survival and to reduce the number of hospitalisations due to worsening heart failure. In addition, BETALOC CR therapy has increased ejection fraction, reduced left ventricular end systolic and end diastolic volumes, improved NYHA functional class and improved Quality of Life.

In the MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) study treatment with metoprolol CR added to standard treatment with ACE inhibitors

and diuretics in patients with decreased LVEF and symptoms of mild to severe chronic heart failure reduced:

- All cause mortality by 34% (p=0.0062 (adjusted); p=0.00009 (nominal))
- Combined endpoint of all cause mortality, and all cause hospitalisation (time to first event) by 19% (p=0.00012)
- Combined endpoint of all cause mortality, and hospitalisation due to worsening heart failure (time to first event ) by 31% (p≤0.00001)
- Combined endpoint of death and heart transplantation (time to first event) by 32% (p=0.0002)
- Cardiovascular death by 38% (p=0.00003)
- Sudden death by 41% (p=0.0002)
- Death from worsening heart failure by 49% (p=0.0023)
- The pooled incidence of cardiac death and non-fatal acute MI by 39% (p≤0.00001)
- Combined endpoint of all cause mortality, hospitalisation due to worsening heart failure, and emergency room (ER) visit due to worsening heart failure (time to first event) by 32% (p≤0.00001)
- The number of hospitalisations due to worsening heart failure by 30% and the number of hospitalisations due to cardiovascular (CV) causes by 15% (p=0.0003).

### **Effect on cardiac rhythm**

BETALOC CR is suitable for regulating the heart rate as it inhibits the cardiac effects of increased sympathetic activity leading to decreased automaticity in the pacemaker cells and reduction of supraventricular conduction velocity. Thus metoprolol controls heart rate in 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.

### **Effect on hyperthyroidism**

Metoprolol reduces the clinical manifestations in hyperthyroidism and can therefore be given as a supplementary medication.

### **Effect on heart disorders with palpitations**

In patients with functional heart disorder with palpitations as a major symptom (which may be due to increased sympathetic activity) BETALOC CR is effective in reducing palpitations and improving the patient's general condition.

### **Effect on migraine**

BETALOC CR is suitable for prophylactic treatment of migraine.

## **5.2 PHARMACOKINETIC PROPERTIES**

### **Absorption and distribution**

BETALOC CR is completely absorbed after oral administration. The systemic bioavailability of metoprolol from a single oral dose is approximately 50%, owing to an extensive first-pass effect. The bioavailability is reduced by about 20-30% for the controlled release preparation compared to the conventional tablets, but this has been demonstrated to be of no significance for clinical efficacy, since the area under the effect curve (AUEC) for heart rate is the same as with conventional tablets. The plasma protein binding of metoprolol is low, approximately 5-10% and has a volume of distribution of 5.6 L/kg.

The controlled release tablet consists of several hundred beads of metoprolol succinate. Each bead is coated with a polymeric membrane which controls the rate of metoprolol release.

The tablet disintegrates rapidly after intake whereby the beads are dispersed in the gastrointestinal tract and release metoprolol continuously for about 20 hours. The elimination half-life of metoprolol averages 3.5 hours. Thus an even metoprolol plasma concentration is achieved over a dosage interval of 24 hours. The release rate is independent of physiological factors such as pH, food and peristalsis.

The rate of elimination is not affected by the formulation but, because of the prolonged absorption phase, administration of the CR tablet results in much less variation in plasma levels and pharmacological effects during a dosing interval compared with the plain tablet.

### **Metabolism and elimination**

Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. The three main metabolites have been identified, though none of them have a clinically significant  $\beta$ -blocking effect.

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 litres/minute and area under the plasma concentration-time curve (AUC) values of up to 6 times higher than in healthy subjects.

The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, paraffin, polyethylene glycol, silicon dioxide, sodium stearyl fumarate and titanium dioxide (E 171).

### **6.2 INCOMPATIBILITIES**

Nil

### **6.3 SHELF-LIFE**

36 months.

### **6.4 SPECIAL PRECAUTION FOR STORAGE**

BETALOC CR 23.75 mg tablets should be stored at or below 30°C.

BETALOC CR 47.5, 90 and 190 mg tablets should be stored at or below 25°C.

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

BETALOC CR 23.75 mg tablets - Blister packs of 30.

BETALOC CR 47.5 mg tablets - Blister packs of 30.

BETALOC CR 95 mg tablets - Blister packs of 30.

BETALOC CR 190 mg tablets - Blister packs of 30

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

Return unused and expired medicines to your local pharmacy for disposal.

## **7. MEDICINE SCHEDULE**

Prescription Medicine.

## 8. SPONSOR

AstraZeneca Limited  
PO Box 87453  
Meadowbank  
Auckland 1742.  
Telephone: (09) 306 5650

## 9. DATE OF FIRST APPROVAL

BETALOC CR 23.75 mg: 1 February 2001  
BETALOC CR 47.5 mg, 95 mg and 190 mg: 19 June 1986

## DATE OF PREPARATION

28 March 2020  
(CDS 130314)

Betaloc is a registered trademark of the AstraZeneca group of companies.

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## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	PO Box amended.