

## NEW ZEALAND DATA SHEET

### 1. AFT-Metoprolol CR (23.75 mg, 47.5 mg, 95 mg and 190 mg controlled-release tablets)

AFT-Metoprolol CR 23.75 mg, 47.5 mg, 95 mg and 190 mg controlled release tablets.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metoprolol – AFT 23.75 mg: Each tablet contains 23.75 mg metoprolol succinate

Metoprolol – AFT 47.5 mg: Each tablet contains 47.5 mg metoprolol succinate

Metoprolol – AFT 95 mg: Each tablet contains 95 mg metoprolol succinate

Metoprolol – AFT 190 mg: Each tablet contains 190 mg metoprolol succinate

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Controlled release tablets.

AFT-METOPROLOL CR tablets 23.75 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 9 mm x 5 mm.

AFT-METOPROLOL CR tablets 47.5 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 11 mm x 6 mm.

AFT-METOPROLOL CR tablets 95 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 16 mm x 8 mm.

AFT-METOPROLOL CR tablets 190 mg are white, oval, biconvex, film-coated tablets scored on both sides. Size 19 mm x 10 mm.

### 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.

#### 4.2 Dose and method of administration

## ***Dose***

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

AFT-METOPROLOL CR is recommended for once daily treatment, should be taken at the same time of the day with regard to food and is preferably taken together with the morning meal. The tablets may be broken in half. AFT-METOPROLOL CR tablets should be swallowed with liquid and 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 AFT-METOPROLOL 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**

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

### **Chronic Heart Failure**

The dose of AFT-METOPROLOL 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 AFT-METOPROLOL CR once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 190 mg AFT-METOPROLOL 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.

### **Myocardial Infarction**

#### **Treatment in the acute stage**

Treatment with metoprolol administered intravenously should be initiated 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).

In patients who tolerate the full intravenous dose (15 mg), AFT-METOPROLOL 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 AFT-METOPROLOL CR 95 mg twice daily for a further 24 hours.

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

### **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.

### **Children**

There is limited experience with metoprolol treatment in children.

## **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 heart 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.
- 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.

AFT-METOPROLOL 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 AFT-METOPROLOL CR interfering with beta2-receptors is less than with conventional tablet formulations of beta1-selective blockers.

The risk of interfering with carbohydrate metabolism or masking hypoglycaemia is likely to be less with AFT-METOPROLOL CR than with conventional tablet formulations of beta1-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, AFT-METOPROLOL CR should be given in lower doses or gradually withdrawn.

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

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

The anaesthetist should be informed that the patient is receiving AFT-METOPROLOL CR prior to surgery. It is not recommended to stop beta-blocker treatment in patients undergoing surgery.

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 AFT-METOPROLOL 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

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 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.

#### **4.6 Fertility, pregnancy and lactation**

##### **Pregnancy**

Category C

As with most medicines, AFT-METOPROLOL CR 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.

##### **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.

#### **4.7 Effects on ability to drive and use machines**

Patients should know how they react to AFT-METOPROLOL CR before they drive or use machines because 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, 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.

\* 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.

**Rare:** Disturbances of cardiac conduction, cardiac arrhythmias.

**Very rare:** Gangrene in patients with pre-existing severe peripheral circulatory disorders.

## **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.

**4.9 Overdose**

**Symptoms**

Overdosage of AFT-METOPROLOL CR may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness / coma, nausea, vomiting and cyanosis. Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patients condition.

The first manifestations of overdosage may be observed 20 minutes to 2 hours after ingestion.

**Treatment**

There is no specific antidote.

On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed:

**Elimination of the Drug:** Induction of vomiting or gastric lavage should be performed.

**Bradycardia:** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

**Hypotension:** A vasopressor should be administered, e.g., levarterenol or dopamine.

**Bronchospasm:** A  $\beta_2$ -stimulating agent and/or a theophylline derivative should be administered.

**Cardiac Failure:** A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Metoprolol is a beta1-selective beta-blocker, i.e. 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.

AFT-METOPROLOL 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 AFT-METOPROLOL 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, AFT-METOPROLOL 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, AFT-METOPROLOL CR in therapeutic doses interferes less than non-selective beta-blockers with the beta<sub>2</sub>-mediated broncho-dilation caused by the beta<sub>2</sub>-agonist.

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

AFT-METOPROLOL CR 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.

## **5.2 Pharmacokinetic properties**

### **Absorption and distribution**

Metoprolol 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.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

ethylcellulose, hydroxypropylmethyl cellulose, methylcellulose, microcrystalline cellulose, glycerol, maize starch, magnesium stearate, stearic acid and titanium dioxide (E 171).

### **6.2 Incompatibilities**

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

The risk of AFT-METOPROLOL 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 AFT-METOPROLOL 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, AFT-METOPROLOL CR should be given in lower doses or gradually withdrawn.

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

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

The anaesthetist should be informed that the patient is receiving AFT-METOPROLOL CR prior to surgery. It is not recommended to stop beta-blocker treatment in patients undergoing surgery.

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 AFT-METOPROLOL 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.

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

### 6.3 Shelf life

Package	Contents	Shelf Life
Blister pack PVC/PE/PVDC-aluminium blister	30 tablets	36 months from date of manufacture stored at or below 25°C.
Blister pack PVC/PE/PVDC-aluminium blister	90 tablets	36 months from date of manufacture stored at or below 25°C.
Blister pack PVC/PE/PVDC-aluminium blister	100 tablets	36 months from date of manufacture stored at or below 25°C
Bottle, plastic, White HDPE with 38 mm child resistant PP cap, induction sealed with aluminium	30 tablets	6 months from date of manufacture stored at or below 25°C.

### 6.4 Special precautions for storage

Protect from light and moisture. Keep out of reach of children. Store below 25 °C.

### 6.5 Nature and contents of container

All strengths of AFT-METOPROLOL CR tablets are available in packs containing 30 and 100 tablets.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MEDICINE SCHEDULE

Prescription medicine.

## 8. SPONSOR

AFT Pharmaceuticals Ltd  
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**9. DATE OF FIRST APPROVAL**

7 August 2008

**10. DATE OF REVISION OF THE TEXT**

February 2019

**SUMMARY TABLE OF CHANGES**

Date	Section(s) Changed	Change (s)
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.