NEW ZEALAND DATA SHEET

1. NAME OF MEDICINE

Topreloc-xl, 23.75 mg, 47.5 mg, 95 mg and 190 mg, modified-release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Topreloc-xl 23.75 mg: Each modified release tablet contains 23.75 mg metoprolol succinate.

Topreloc-xl 47.5 mg: Each modified release tablet contains 47.5 mg metoprolol succinate.

Topreloc-xl 95 mg: Each modified release tablet contains 95 mg metoprolol succinate.

Topreloc-xl 190 mg: Each modified release tablet contains 190 mg metoprolol succinate.

Excipient with known effect: None

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Topreloc-xl 23.75 mg: White to off white, oval shape, biconvex film coated tablet with breakline on one side and debossed with ‘A’ and ‘3’ on each side of breakline on other side.

Topreloc-xl 47.5 mg: White to off white, round shape, biconvex film coated tablet with breakline on one side and debossed with ‘A50’ on other side.

Topreloc-xl 95 mg: White to off white, round shape, biconvex film coated tablet with breakline on one side and debossed with ‘A100’ on other side.

Topreloc-xl 190 mg: White to off white, oval shape, biconvex film coated tablet with breakline on one side and debossed with ‘A200’ on other side.

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.
Topreloc-xl is intended for once-daily treatment and can be taken with or without food. The Topreloc-xl 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 Topreloc-xl 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. Topreloc-xl can be combined with other antianginal agents if needed.

Chronic heart failure

The dose of Topreloc-xl 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 Topreloc-xl once daily (or to the highest tolerated dose). During long-term treatment the aim should be to reach 190 mg Topreloc-xl 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 ≥ 6 years is 0.95 mg/kg Topreloc-xl, 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.

Topreloc-xl 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 Topreloc-xl 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 Topreloc-xl 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, Topreloc-xl should be given in lower doses or gradually withdrawn.

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

Where Topreloc-xl 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 Topreloc-xl, 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 Topreloc-xl 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 betablockers, 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 betablockers.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

As with most medicines, Topreloc-xl 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 betablocking 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 metoprolol succinate before they drive or use machines because occasionally dizziness or fatigue may occur.

4.8 UNDESIRABLE EFFECTS

Metoprolol succinate 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 (≥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 stock 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 α_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

5.1 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.

Metoprolol succinate gives an even plasma concentration time and effect profile (beta1-blockade) over 24 hours in contrast to conventional tablet formulations of beta1-selective blockers.

Due to the lack of pronounced peaks in plasma concentration, the clinical beta1-selectivity is improved with the Metoprolol succinate formulation when compared to the conventional tablet formulations of beta1-selective blockers. Furthermore the potential risk for peak plasma concentration related side-effects, such as bradycardia and leg fatigue is reduced.

When mandatory, Metoprolol succinate, 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 succinate in therapeutic doses interferes less than non-selective beta-blockers with the beta2-mediated bronchodilation caused by the beta2-agonist.

Metoprolol succinate interferes less with insulin release and carbohydrate metabolism than do nonselective beta-blockers.

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

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

CLINICAL EFFICACY AND SAFETY

Effect in hypertension

Metoprolol succinate 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, Metoprolol succinate has been shown in a 4–week study to reduced 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 (≤0.40) Metoprolol succinate 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, Metoprolol succinate 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

Metoprolol succinate 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) Metoprolol succinate is effective in reducing palpitations and improving the patient's general condition.

Effect on migraine

Metoprolol succinate is suitable for prophylactic treatment of migraine.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution

Metoprolol succinate 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 metoprolol 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 β-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

Each Topreloc-xl Tablet Contains:

- microcrystalline cellulose
- silicon dioxide
- povidone
- ethylcellulose
- methacrylic acid copolymer
- triethyl citrate
- macrogol 6000
- silicified microcrystalline cellulose
- croscarmellose sodium
- sodium stearylfumarate
- purified talc
- opadry complete film coating system YS-1R-7006 Clear (ARTG PI No. 13068)
- opadry complete film coating system 02F280014 (ARTG PI No. 123088)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

24 months (for blister pack and HDPE bottle pack)

In-use shelf life (for HDPE bottle packs only) - 3 months at 25 °C from the date of opening.

6.4 SPECIAL PRECAUTION FOR STORAGE

Store below 25°C.Protect from moisture

6.5 NATURE AND CONTENTS OF CONTAINER

<u>23.75 mg:</u>

- PVC/PVDC/Al blister packs containing 15 tablets
- HDPE Bottles with polypropylene child-resistant screw caps containing

15, 30 & 90 tablets.

47.5 mg/95 mg/190 mg:
- PVC/PVDC/Al blister packs containing 15 & 30 tablets
- HDPE Bottles with polypropylene child-resistant screw caps containing 15, 30 & 90 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pharmacor Limited
c/- Wynn Williams
Level 25, Vero Centre
48 Shortland Street
Auckland Central
AUCKLAND 1010
New Zealand
Ph: +64 800 172 553 or 0800 172 553

9. DATE OF FIRST APPROVAL

22 December 2025

10. DATE OF PREPARATION

22 December 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information