# NEW ZEALAND DATA SHEET

## 1 PRODUCT NAME

Lopresor® 50 mg tablet

Lopresor® 100 mg tablet

Lopresor® 5 mg/5 mL solution for injection

Slow Lopresor® 200mg Modified release tablet

(*metoprolol tartrate*)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is Di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol] L(+)-tartrate (metoprolol tartrate).

Metoprolol is an aryloxypropanolamine derivative.

One 5 mL ampoule contains 5 mg metoprolol tartrate. One tablet contains 50 mg, 100 mg or 200 mg metoprolol tartrate.

For a full list of excipients, see Section 6.1 List of excipients.

## 3 PHAMACEUTICAL FORM

### Lopresor Tablet 50mg

Pink heart shaped film-coated tablet with slightly convex faces.
Imprints: CIBA on one side and HM on other side.

### Lopresor Tablet 100mg

Light blue, heart shaped, film-coated tablet with slightly convex faces.
Imprints: CIBA on one side and I/P with score on other side.

### Lopresor 5mg/5ml solution injection

Clear colourless liquid contained in a 1 point glass ampoule.

### Slow-Lopresor Tablet 200mg

Divitabs or scored sustained-release tablets of 200 mg.

Light yellow, capsule shaped, film-coated tablet with convex faces, slightly bevelled edges, and a deep breaking score on both sides.
Imprints: CG/CG on one side and CDC/CDC on other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

<u>All forms</u>

Disturbances of cardiac rhythm, including supraventricular and ventricular arrhythmias.

<u>Oral forms only</u>

Hypertension: as monotherapy or for use in combination with other antihypertensives, for example, a diuretic, peripheral vasodilator or angiotensin converting-enzyme (ACE) inhibitor.

Angina pectoris: For long-term prophylaxis. Nitroglycerin should be used, if necessary, for alleviating acute attacks.

Hyperthyroidism (as adjunctive medication*)*.

Functional heart disorders with palpitation.

Prevention of migraine.

## 4.2 Dose and method of administration

Parenteral administration of Lopresor should be supervised by experienced staff in a setting in which monitoring and resuscitating equipment are available. For oral treatment, the tablets should be swallowed unchewed.

The dosage should be adapted to the requirements of the individual patient. The following dosage recommendations may be taken as a guide:

### Disturbances of cardiac rhythm

Ampoules: The starting dose is 5 mg, injected slowly intravenously (1 to 2 mg/min). The injection can be repeated at 5-minute intervals until a satisfactory clinical response has been obtained. A total dose of 10 to 15 mg generally proves sufficient; increasing the dose to 20 mg or more does not usually yield better results. “Use immediately after opening. Discard any unused portion”.

Tablets: The daily dose is 100 to 150 mg, given in 2 or 3 divided doses; if necessary, the daily dose can be increased to 300 mg.

### Hypertension

The daily oral dose is 100 to 200 mg, given either as a single dose in the morning or as 2 divided doses (morning and evening). If necessary, another antihypertensive can be prescribed in addition (see Section 4.5 Interaction with other medicines and other forms of interaction).

Divitabs (fractionable sustained-release tablets): 1 of the Divitabs early in the morning. If necessary, another antihypertensive can be prescribed in addition. In mild hypertension, ½ of one of the Divitabs taken early in the morning may suffice.

### Angina pectoris

The daily oral dose is 100 to 200 mg, given in 2 divided doses; if necessary, the daily dose can be increased to 400 mg.

Divitabs: ½ or 1 of the Divitabs early in the morning; if necessary, this dose can be repeated in the evening.

### Hyperthyroidism

The daily oral dose is 150 to 200 mg (may be increased up to 400 mg), given in 3 or 4 divided doses.

### Functional heart disorders with palpitation

The daily oral dose is 100 mg, given as a single dose in the morning; if necessary, the daily dose can be increased to 200 mg, given in 2 divided doses (morning and evening).

Divitabs: ½ of one of the Divitabs daily, given in the morning; if necessary, the daily dosage can be raised to 1 of the Divitabs, to be taken also as a single dose in the morning.

### Prevention of migraine

The daily oral dose is 100 mg, given as a single dose in the morning; if necessary, the daily dose can be increased to 200 mg, given in 2 divided doses (morning and evening)

Divitabs: ½ of one of the Divitabs daily, given in the morning; if necessary, the daily dosage can be raised to 1 of the Divitabs, to be taken also as a single dose in the morning.

### Paediatric patients

No studies have been performed in paediatric patients. The safety and efficacy of Lopresor and Slow Lopresor in paediatric patients have not been established.

### Hepatic impairment

Lopresor blood levels are likely to increase substantially in patients with hepatic impairment. Therefore, Lopresor or Slow Lopresor should be initiated at low doses with cautious gradual dose titration according to clinical response.

### Geriatric patients (>65 years)

No dose adjustment of Lopresor or Slow Lopresor is required in geriatric patients but it should be given with caution due to increased likelihood of adverse events.

## 4.3 Contraindications

Hypersensitivity to metoprolol and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur).

- Atrioventricular block of second or third degree.
- Decompensated heart failure.
- Clinically relevant sinus bradycardia (heart rate less than 45 to 50 beats/min).
- Sick-sinus syndrome.
- Severe peripheral arterial circulatory disorders.
- Cardiogenic shock.
- Untreated phaechromocytoma (see Section 4.4 Special warnings and precautions for use).
- Hypotension.

**For oral use**: severe bronchial asthma or history of severe bronchospasm (see Section 4.4 Special warnings and precautions for use).

**For intravenous use**: bronchial asthma and history of bronchospasm.

Use of Lopresor or Slow Lopresor is contraindicated in patients with myocardial infarction who have a heart rate of less than 45 to 50 beats/min, P-R interval of greater than 0.24 sec, a systolic blood pressure of less than 100 mmHg, and/or severe heart failure.

## 4.4 Special Warnings and precautions for use

Adverse drug reactions (or constellations of reactions)

*Bronchospastic diseases*

In general, patients with bronchospastic diseases should not be given beta-blockers, including Lopresor or Slow Lopresor. However, because of its relative cardioselectivity, oral Lopresor or Slow Lopresor may be administered with caution to patients with mild or moderate bronchospastic diseases who do not respond to, or cannot tolerate, other suitable treatments. Since $beta_1$-selectivity is not absolute, a $beta_2$-agonist should be administered concomitantly, and the lowest possible dose of Lopresor or Slow Lopresor should be used.

*Diabetic patients*

Lopresor or Slow Lopresor should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents (see Section 4.5 Interaction with other medicines and other forms of interaction).. Diabetic patients should be warned that beta-blockers, including Lopresor or Slow Lopresor, may mask the tachycardia occurring with hypoglycaemia; however, other manifestations of hypoglycaemia such as dizziness and sweating may not be significantly suppressed, and sweating may be increased.

*Cardiovascular system*

Beta-blockers, including Lopresor or Slow Lopresor, should not be used in patients with untreated congestive heart failure (see Section 4.3 Contraindications). This condition should first be stabilised.

Because of their negative effect on atrioventricular conduction, beta-blockers, including Lopresor or Slow Lopresor, should be given only with caution to patients with first degree atrioventricular block (see Section 4.3 Contraindications).

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/min), the dosage should be gradually reduced, or treatment gradually withdrawn (see Section 4.3 Contraindications).

*Myocardial infarction*

In patients with myocardial infarction, if significant hypotension occurs, Lopresor or Slow Lopresor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Intensive hemodynamic monitoring may be required and appropriate treatment modalities should be instituted. If hypotension is associated with significant bradycardia or atrioventricular block, treatment should be directed at reversing these.

*Peripheral circulatory disorders*

Lopresor or Slow Lopresor should be used with caution in patients with peripheral arterial circulatory disorders (for example, Raynaud's disease or phenomenon, intermittent claudication), because beta-blocker treatment may aggravate such conditions (see Section 4.3 Contraindications).

*Pheochromocytoma*

In patients known to have, or suspected of having, a phaeochromocytoma, Lopresor or Slow Lopresor should always be given in combination with an alpha-blocker and only after the alpha-blocker has been initiated (see Section 4.3 Contraindications).

*Anesthesia and surgery*

The necessity, or desirability, of withdrawing beta-blocking agents, including Lopresor or Slow Lopresor, prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. The benefits of continuing a treatment with a beta-blocker, including Lopresor, or Slow Lopresor should be balanced against the risk of withdrawing it in each patient. If a patient treated with Lopresor or Slow Lopresor needs general anaesthesia, the anaesthetist should be informed that the patient is receiving a beta-blocker. An

anaesthetic agent with as little cardiodepressant effect as possible should be used (see Section 4.5 Interaction with other medicines and other forms of interaction). If it is thought necessary to withdraw beta-blocker, including Lopresor or Slow Lopresor, therapy before surgery, this should be done gradually and completed about 48 hours before the general anaesthetic.

### *Abrupt withdrawal*

Lopresor or Slow Lopresor treatment should not be stopped suddenly, especially in patients with ischaemic heart disease. To prevent exacerbation of angina pectoris, the dosage should be gradually reduced over 1 to 3 weeks and, if necessary, replacement therapy should be initiated at the same time.

### *Anaphylactic reactions*

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers, including Lopresor or Slow Lopresor, should be avoided for patients who are at increased risk of anaphylaxis.

### *Prinzmetal's angina*

Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). Relatively selective $beta_1$-receptor blockers, such as Lopresor or Slow Lopresor, can be used in such patients, but only with the utmost care.

### *Thyrotoxicosis*

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, where Lopresor or Slow Lopresor is administered to patients having, or suspected of developing, thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

### *Oculomucocutaneous syndrome*

The full oculomucocutaneous syndrome, as described elsewhere with practolol, has not been reported with Lopresor or Slow Lopresor. However, part of this syndrome (dry eyes either alone or, occasionally, with skin rashes) has occurred. In most cases the symptoms cleared when Lopresor or Slow Lopresor treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, gradual discontinuation of Lopresor or Slow Lopresor should be considered.

## Interactions

Calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving Lopresor or Slow Lopresor because there is a risk of cardiac arrest in this situation (see Section 4.5 Interaction with other medicines and other forms of interaction).

## Special populations

### *Hepatic impairment*

Metoprolol undergoes substantial hepatic first-pass metabolism, and is mainly eliminated by hepatic metabolism (see Section 5 Pharmacological properties, and 5.2 Pharmacokinetic properties). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations.

### *Geriatric patients*

Elderly patients should be treated cautiously. An excessive decrease in blood pressure or pulse rate may reduce the blood supply to vital organs to inadequate levels.

## 4.5 Interaction with other medicines and other forms of medicines

Observed interactions resulting in concomitant use not being recommended

*Calcium channel blockers (IV use)*

Calcium channel blockers such as verapamil and diltiazem may potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and atrioventricular conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving Lopresor or Slow Lopresor because there is a risk of cardiac arrest in this situation (see Section 4.4 Special warnings and precautions for use)

*Other antihypertensive drugs*

The effects of Lopresor or Slow Lopresor and other antihypertensive drugs on blood pressure are usually additive. Patients receiving concurrent treatment with catecholamine depleting drugs, other beta-blockers (including those in form of eye drops, such as timolol), or monoamine oxidase (MAO) inhibitors, should be carefully monitored. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

*Calcium channel blockers (oral use)*

Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium channel blocker of the verapamil type in combination with Lopresor or Slow Lopresor should be closely monitored.

*Anti-arrhythmic drugs*

Beta-blockers may potentiate the negative inotropic effect of anti-arrhythmic agents and their effect on atrial-conduction time. Particularly, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest, and atrioventricular block anti-arrhythmic agents such as quinidine tocainide, procainamide, ajmaline amiodarone, flecainide and disopyramide may potentiate the effects of Lopresor or Slow Lopresor on heart rate and atrioventricular conduction.

*Nitroglycerin*

Nitroglycerin may enhance the hypotensive effect of Lopresor or Slow Lopresor.

*Other drugs causing decrease in heart rate*

Concomitant administration of beta-blockers with other drugs known to decrease heart rate such as sphingosine-1-phosphate receptor modulators (e.g. fingolimod) may result in additive heart rate lowering effects.

*Other drugs causing decrease in blood pressure*

Concomitant administration of beta-blockers with other drugs known to decrease blood pressure such as aldesleukin may result in an enhanced hypotensive effect.

*General anaesthetics*

Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers (see Section 4.4 Special warnings and precautions for use).

*CYP2D6 inhibitors*

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer phenocopying, (see Section 5.2 Pharmacokinetic properties). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine,

desipramine antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine.

### *Hydralazine*

Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.

### *Digitalis glycosides*

Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time. Monitoring heart rate and PR interval is recommended.

### *Sympathomimetics*

Concomitant administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including antitussives or nose and eye drops) with a beta-blocker may enhance the pressor response resulting in hypertension due to mutual inhibition of therapeutic effects. However, this is less likely with therapeutic doses of $beta_1$-selective drugs than with non-selective beta-blockers.

### *Non-steroidal anti-inflammatory drugs*

Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker may decrease the antihypertensive effect of metoprolol, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by non-steroidal anti-inflammatory drugs.

### *Hepatic enzyme inducers*

Enzyme-inducing drugs may affect plasma concentrations of metoprolol. For example, the plasma concentration of metoprolol is lowered by rifampicin.

### *Anti-adrenergic agents*

Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers. Beta- adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia. On the contrary, beta adrenergic blockers may also potentiate the hypertensive response to withdrawal of clonidine as patients receiving concomitant clonidine and beta-adrenergic blocker. If a patient is treated with clonidine and Lopresor or Slow Lopresor concurrently, and clonidine treatment is to be discontinued, Lopresor or Slow Lopresor should be stopped several days before clonidine is withdrawn.

### *Antidiabetic drugs and insulin*

Beta-blockers may interfere with the usual hemodynamic response to hypoglycemia and produce a rise in blood pressure associated with severe bradycardia In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a $beta_1$-selective drug such as Lopresor or Slow Lopresor than with a non-selective beta-blocker. However, diabetic patients receiving Lopresor or Slow Lopresor should be monitored to ensure that diabetes control is maintained (see also Section 4.4 Special warnings and precautions for use).

### *Lidocaine (xylocaine)*

Metoprolol may reduce the clearance of lidocaine, leading to increased lidocaine effects.

*Prazosin*

The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker, including Lopresor or Slow Lopresor.

*Ergot alkaloid*

Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

*Dipyridamole*

In general, administration of a beta- blocker should be withheld before dipyridamole testing, with careful monitoring of heart rate following the dipyridamole injection.

*Alcohol*

Metoprolol may modify the pharmacokinetic parameters of alcohol.

## 4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor.

*Pregnancy*

In general, no drug should be taken during the first 3 months of pregnancy, and the relative benefits and risks of treatment should be carefully considered throughout pregnancy.

There is a limited amount of data on the use of metoprolol in pregnant women. Experience with metoprolol in the first trimester of pregnancy is limited, but no fetal malformations attributable to metoprolol have been reported. However, beta-blockers may reduce placental perfusion.

In the case of treatment with Lopresor or Slow Lopresor during the pregnancy the lowest possible dose should be used, and treatment should be discontinued at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn baby (for example, bradycardia, hypoglycaemia).

*Lactation*

Small quantities of metoprolol are secreted into breast milk: with therapeutic doses, an infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of metoprolol. Nevertheless, breast-fed infants should be closely observed for signs of beta-blockade.

## 4.7 Effects on ability to drive and use machines

Dizziness, fatigue or visual impairment may occur during treatment with Lopresor or Slow Lopresor (see Section 4.8 Undesirable effects), and may adversely affect the patient's ability to drive or use machines.

## 4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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); very rare (<1/10,000).

Adverse drug reactions from clinical trials

| | |
|---|---|
| **Blood and the lymphatic system disorders** | |
| Very rare | thrombocytopenia |
| **Psychiatric disorders** | |
| Rare | depression, nightmares |
| Very rare | personality disorder, hallucinations |
| **Nervous system disorders** | |
| Common | dizziness, headache |
| Rare | depressed level of consciousness, somnolence or insomnia, paraesthesia |
| **Eye disorders** | |
| Very rare | visual impairment (e.g. blurred vision), dry eyes, eye irritation |
| **Ear and labyrinth disorders** | |
| Very rare | tinnitus[1] hearing disorders (e.g. hypoacusis or deafness) |
| **Cardiac disorders** | |
| Common | bradycardia |
| Rare | cardiac failure, arrhythmias, palpitation |
| Very rare | conduction disorders, chest pain |
| **Vascular disorders** | |
| Common | orthostatic hypotension (occasionally with syncope) |
| Rare | oedema, Raynaud's phenomenon |
| Very rare | Gangrene[2] |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common | exertional dyspnoea |
| Rare | Bronchospasm[3] |
| Very rare | rhinitis |
| **Gastrointestinal disorders** | |
| Common | nausea and vomiting, abdominal pain |
| Rare | diarrhoea or constipation |
| Very rare | dry mouth, retroperitoneal fibrosis[4] |
| **Hepatobiliary disorders** | |
| Very rare | hepatitis |
| **Skin and subcutaneous tissue disorders** | |
| Rare | rash (in the form of urticaria, psoriasiform and dystrophic skin lesions) |
| Very rare | Photosensitivity reaction, hyperhydrosis, alopecia, worsening of psoriasis. |

| | |
|---|---|
| **Musculoskeletal, connective tissue disorders** | |
| Rare | muscle spasms |
| Very rare | arthritis |
| **Reproductive system and breast disorders** | |
| Very rare | erectile dysfunction, libido disorder, Peyronie's disease[4] |
| **General disorders and administration site conditions** | |
| Common | fatigue |
| **Investigations** | |
| Very rare | weight increase, liver function test abnormalities |

1 and, in doses exceeding those recommended
2 in patients with pre-existing severe peripheral circulatory disorders
3 which may occur in patients without a history of obstructive lung disease
4 relationship to Lopresor has not been definitely established

Adverse drug reactions from spontaneous reports and literature cases (frequency not known). The following adverse reactions have been derived from post-marketing experience with Lopresor via spontaneous case reports and literature cases: Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

### Adverse drug reactions from spontaneous reports and literature (frequency not known)

**Nervous system disorders**

confusional state

**Investigations**

blood triglycerides increased, High Density Lipoprotein (HDL) decreased

### Reporting of suspected adverse reactions

Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorization 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 via https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

### Signs and symptoms

An overdosage of Lopresor or Slow Lopresor may lead to severe hypotension, sinus bradycardia, atrioventricular block, myocardial infarction, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting, and cyanosis and death.

Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravates the signs and symptoms.

The first manifestations of overdose appear 20 minutes to 2 hours after ingestion of Lopresor or Slow Lopresor. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

### Management

Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate. Even apparently well patients who have taken a small overdose should be closely observed for signs of poisoning for at least 4 hours.

In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage (if within 4 hours after ingestion of Lopresor or Slow Lopresor) and/or activated charcoal to remove the drug from the gastrointestinal tract. Haemodialysis is unlikely to make a useful contribution to metoprolol elimination.

Atropine may be given intravenously to control significant bradycardia. Intravenous beta-agonists such as prenalterol or isoprenaline should be used to treat bradycardia and hypotension; very high doses may be needed to overcome the beta-blockade. Dopamine, dobutamine or noradrenaline may be given to maintain blood pressure. Glucagon has positive inotropic and chronotropic effects on the heart that are independent of beta-adrenergic receptors, and has proved effective in the treatment of resistant hypotension and heart failure associated with beta-blocker overdose.

Diazepam is the drug of choice for controlling seizures. A $beta_2$-agonist or aminophylline can be used to reverse bronchospasm; patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

The beta-blocker withdrawal phenomenon (see Section 4.4 Special warnings and precautions for use) may occur after overdose.

For advice on the management of overdose please contact the National Poisons Centre 0800 POISON (0800 764766).

# **5** PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Cardioselective beta-blocker, ATC code: C07A B02

### Mechanism of action (MoA)

Metoprolol is a cardioselective beta-blocker; it blocks $beta_1$-adrenergic receptors (which are mainly located in the heart) at lower doses than those needed to block $beta_2$-receptors, which are mainly located in the bronchi and peripheral vessels. It has no membrane-stabilising effect nor partial agonist (intrinsic sympathomimetic) activity.

### Pharmacodynamics properties

The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility, and cardiac output.

Metoprolol lowers elevated blood pressure in the standing and lying position. It also reduces the rise in blood pressure occurring in response to exercise. Treatment results in an initial increase in peripheral vascular resistance, which during long-term administration is normalised or, in some cases, reduced. As with all beta-blockers, the precise mechanism of the antihypertensive effect of metoprolol is not fully understood. However, the long-term reduction blood pressure seen with metoprolol appears to parallel this gradual decrease in total peripheral resistance.

In patients with angina pectoris, metoprolol reduces the frequency and severity of ischaemic episodes and increases physical working capacity. These beneficial effects may be due to decreased myocardial oxygen demand as a result of the reduced heart rate and myocardial contractility.

In patients with supraventricular tachycardia, atrial fibrillation, or ventricular extrasystoles or other ventricular arrhythmias, metoprolol has a regulating effect on the heart rate. Its anti-arrhythmic action is due primarily to inhibition of the automaticity of pacemaker cells and to prolongation of atrioventricular conduction.

In patients with a suspected or confirmed myocardial infarction, metoprolol lowers mortality. This effect may possibly be attributable to a decrease in the incidence of severe ventricular arrhythmias, as well as to limitation of infarct size. Metoprolol has also been shown to reduce the incidence of non-fatal myocardial reinfarction.

Through its beta-blocking effect, metoprolol is suitable for the treatment of functional heart disorders with palpitation, for the prevention of migraine, and adjunctive treatment of hyperthyroidism.

Long-term treatment with metoprolol may reduce insulin sensitivity. However, metoprolol interferes with insulin release and carbohydrate metabolism less than non-selective beta-blockers.

In short-term studies it has been shown that metoprolol may alter the blood lipid profile. It may cause an increase in triglycerides and a decrease in free fatty acids; in some cases, a small decrease in the high-density lipoprotein (HDL) fraction has been observed, although to a lesser extent than with non-selective beta-blockers. In one long-term study lasting several years, cholesterol levels were found to be reduced.

Pharmacokinetic and pharmacodynamic studies indicate that 30% of maximum beta-1-adrenoreceptor antagonistic activity is essential for minimum pharmacodynamic effect which is observed with about 45 nmol/L metoprolol in plasma.

## 5.2 Pharmacokinetics properties

### Absorption

Following oral administration of conventional tablet, metoprolol is rapidly and almost completely absorbed from the gastrointestinal tract. The drug is absorbed evenly throughout gastrointestinal tract .Absorption of metoprolol from with Slow Lopresor or Slow Lopresor tablets, absorption is slower, but the availability of metoprolol is similar compared with conventional tablets. Peak plasma concentrations are attained after approximately 1.5 to 2 hours with conventional metoprolol tablets, and after approximately 4 to 5 hours with sustained-release tablets. Plasma concentrations of metoprolol increase approximately in proportion with the dose in the 50-mg to 200-mg dose range. Owing to extensive hepatic first-pass metabolism, approximately 50% of a single oral dose of metoprolol reaches the systemic circulation. The extent of presystemic elimination differs between individuals because of genetic differences in oxidative metabolism. Although the plasma profiles exhibit wide intersubject variability, they are reproducible within an individual. Following repeated administration, the percentage of the dose systemically available is approximately 40% higher than after a single dose (that is, approximately 70%). This may be due to partial saturation of the first-pass metabolism, or reduced clearance as a result of reduced hepatic blood flow. Ingestion with food may increase the systemic availability of a single oral dose by approximately 20% to 40%.

After intravenous injection metoprolol is very rapidly distributed with a half-life of 5 to 15 min. Within the dose range of 10 to 20 mg, the plasma concentrations rise linearly in relation to the size of the dose. Metoprolol exhibits stereo-specific pharmacokinetics.

### Distribution

Metoprolol is extensively and rapidly distributed, with a reported volume of distribution of 3.2 to 5.6 L/kg. The apparent volume of distribution at steady-state (Vss) in extensive metabolizers (4.84 L/kg) is relatively higher than poor metabolizers (2.83 L/kg). The half-life is not dose-dependent and does not change on repeated dosing. Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk (see Section 4.6 Fertility, pregnancy and lactation). In patients with hypertension, metoprolol concentrations in cerebrospinal fluid are similar to those in

plasma. Metoprolol is not a significant P-glycoprotein substrates indicating that inter-individual variability in pharmacokinetics of metoprolol can be majorly due to CYP2D6 metabolism.

## Biotransformation/ Metabolism

Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The main metabolic pathways of metoprolol are alpha-hydroxylation, O-demethylation, and oxidative deamination. Alpha-hydroxylation of metoprolol is stereo-selective. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). However, the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol contribute significantly to its beta-blocking effect.

## Elimination

The average elimination half-life of metoprolol is 3 to 4 hours; in poor metabolisers the half-life may be 7 to 9 hours. Following single oral administration of 100 mg metoprolol the median clearance were 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultra-rapid metabolizers, respectively. The renal clearance of the stereo-isomers does not exhibit stereo-selectivity in renal excretion. Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolisers), less than 5% of an oral dose, and less than 10% of an intravenous dose, is excreted as unchanged drug. In poor metabolisers, up to 30% or 40% of oral or intravenous doses, respectively, may be excreted unchanged. The total plasma clearance of metoprolol after intravenous administration is approximately 1 L/min.

## Dose proportionality

Metoprolol exhibits saturable pre-systemic metabolism leading to non-proportionate increase in the exposure with increased dose. However, a dose propionate pharmacokinetics is expected with extended release formulations.

## Food effect

Food appeared to increase the rate of absorption of metoprolol leading to a slightly higher maximum plasma concentration at earlier time. However, it does not impact significantly on the clearance or the time at which the maximum peak concentration is observed (Tmax).

In order to minimize the effect-variations within the individual, it is recommended that Lopresor should always be taken in standardized relation with food: If physician ask the patient to take Lopresor either before the breakfast or with the breakfast then the patient should continue taking Lopresor with same schedule during the course of therapy.

Slow Lopresor can be taken with or without meals preferably in the morning.

## Special population

### *Geriatric patients*

The geriatric population may show slightly higher plasma concentrations of metoprolol as a combined result of a decreased metabolism of the drug in elderly population and a decreased hepatic blood flow. However, this increase is not clinically significant or therapeutically relevant. Metoprolol does not accumulate on repeated administration and there is no necessity of dosage adjustment in elderly population.

### *Patients with renal impairment*

Pharmacokinetics of metoprolol is not impacted in patient with renal impairment. However, there is a possibility of accumulation of one of its less active metabolite in patients with a creatinine clearance below 5 mL/min, and this accumulation would not influence the beta-blocking properties of metoprolol. Patients with renal impairment may usually be treated with normal dose.

### *Patients with hepatic impairment*

Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment may impact the pharmacokinetics of metoprolol. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h), in patients with liver impairment. Patients with a portacaval anastomosis.

Patients with a portacaval anastomosis had a systemic clearance of an intravenous dose of approximately 0.3 L/min and area under concentration-time curve (AUC) values up to 6-fold higher than those in healthy subjects.

### *Patients with inflammatory disease*

Inflammatory disease has no effect on the pharmacokinetics of metoprolol.

### *Patients with hyperthyroidism*

Hyperthyroidism may increase the presystemic clearance of metoprolol.

### *Ethnic sensitivity*

The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizer phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolizers. CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizer with normal CYP2D6 activity.

## 5.3 Preclinical safety data

### Reproductive toxicity

Reproduction toxicity studies in mice, rats and rabbits did not indicate teratogenic potential for metoprolol tartrate. High doses were associated with some maternal toxicity, and growth delay of the offspring both in utero and after birth. There was no evidence of impaired fertility in rats at oral doses up to 500 mg/kg.

### Mutagenicity

Metoprolol tartrate was devoid of mutagenic/genotoxic potential in the bacterial cell system (Ames) test and in vivo assays involving mammalian somatic cells or germinal cells of male mice.

### Carcinogenicity

Metoprolol tartrate was not carcinogenic in mice and rats after oral administration of doses up to 800 mg/kg for 21 to 24 months.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

### Lopresor

**Solution for injection**:

Sodium chloride,

water for injection.

**Tablets of 50 mg**:

Silica aerogel,

cellulose,

lactose,
magnesium stearate,
polyvinylpyrrolidone,
sodium carboxymethyl starch,
hydroxypropyl methylcellulose,
red iron oxide (E 172),
polysorbate 80,
talc,
titanium dioxide (E 171).

**Tablets of 100 mg**:
Silica aerogel,
cellulose,
magnesium stearate,
sodium carboxymethyl starch,
hydroxypropyl methylcellulose,
polyvinylpyrrolidone,
shellac,
indico carmine,
titanium dioxide (E 171).

Slow Lopresor

**Divitabs (divisible sustained-release tablets) of 200 mg:**
Silica aerogel,
cellulose,
dibasic calcium phosphate,
copolymer based on polyacrylic/methacrylic esters,
magnesium stearate,
hydroxypropyl methylcellulose,
glycol palmitostearate,
yellow iron oxide (E 172),
polysorbate 80,
talc,
titanium dioxide (E 171).

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Ampoules: 5 years

Tablets of 50 mg and 100 mg: 3 years
Slow Lopresor of 200 mg: 5 years

### 6.4 Special precautions for storage

Ampoules: Protect from light. Store at or below 25°C
Tablets 50 mg: Protect from moisture and heat (store below 30° C).
Tablets 100 mg: Protect from moisture (store below 30° C).
Slow Lopresor 200mg: Special storage requirements

Lopresor and Slow Lopresor should be kept out of the reach and sight of children.

### 6.5 Nature and contents of container

Lopresor 50mg: bottles containing 100 tablets
Lopresor 100mg: bottles containing 60 tablets
Slow Lopresor 200mg: blisters containing 28 tablets

Not all pack sizes may be marketed.

### 6.6 Special Instructions for use and handling

There are no specific instructions for use/handling.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

Novartis New Zealand Limited

PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

® Registered trademark of Novartis

## 9 DATE OF FIRST APPROVAL

9 September 1976

## 10 DATE OF REVISION OF THE TEXT

31 August 2020

### SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| Section 8 - SPONSOR | Removed Sponsor's old address |

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