AUSTRALIAN PRODUCT INFORMATION – NOUMED METOPROLOL 50mg and 100 mg tablets

(metoprolol tartrate)

1. NAME OF THE MEDICINE

Metoprolol tartrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Noumed Metoprolol tablet contain 50mg or 100 mg of metoprolol tartrate.

List of excipients with known effect: lactose monohydrate.

For the full list of excipients, see *section 6.1 List of excipients*.

3. PHARMACEUTICAL FORM

Noumed Metoprolol 50 mg Tablets: White, round, biconvex, with a score notch on one side.

Noumed Metoprolol 100 mg Tablets: White, round, biconvex, with a score notch on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension; angina pectoris; suspected or definite myocardial infarction; migraine prophylaxis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Noumed Metoprolol is recommended for oral therapy in hypertension, angina pectoris, suspected or definite myocardial infarction and migraine prophylaxis.

Hypertension

Initially: Mild hypertension: 50 or 100 mg once daily for one week.

Severe hypertension: 50 or 100 mg twice daily for one week.

Maintenance: 50 or 100 mg once or twice daily.

Some patients will respond to 50 mg once daily. However, a large number of patients will respond to 100 mg once daily as initial and maintenance therapy. Response is rarely improved by increasing the dose beyond 200 mg daily. The maximum daily dose should not exceed 400 mg. Although twice daily dosage is optimal in patients where maintenance dosage is 150 mg daily or less, it may be administered as a single dose.

Angina Pectoris

50 to 100 mg two or three times daily.

Myocardial infarction

Initially: Therapy should commence with Noumed Metoprolol 50 mg tablets twice daily and be continued for 48 hours.

Maintenance: The oral maintenance dose is generally 100 mg twice daily.

Migraine prophylaxis

100 to 150 mg given in divided doses morning and evening.

4.3 CONTRAINDICATIONS

- Severe bronchial asthma or history of severe ronchospasm. β-Adrenergic blockade of the smooth muscle of bronchioles may result in an increased airways resistance. These medicines also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

  Therefore, β-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective β-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Right ventricular failure secondary to pulmonary hypertension.
- Significant right ventricular hypertrophy.
- Sinus bradycardia (less than 45 to 50 beats/minute).
- Second and third degree atrioventricular block.
- Shock (including cardiogenic and hypovolaemic shock).
- Hypersensitivity to metoprolol tartrate and related derivatives.
- Hypersensitivity to any of the excipients in Noumed Metoprolol (see *section 6.1 List of excipients*)
- Sensitivity to other β-blockers as cross sensitivity between β-blockers can occur.
- Non-compensated congestive heart failure (see *section 4.4 Special warnings and precautions for use*).
- Sick-sinus syndrome.
- Severe peripheral arterial circulatory disorders.
- Myocardial infarction patients with a heart rate of < 45 beats/minute, a PR interval of > 0.24 seconds, a systolic blood pressure of < 100mmHg and/or moderate to severe non-compensated heart failure.
- Hypotension.
- Untreated phaeochromocytoma (see *section 4.4 Special warnings and precautions for use*).
- Continuous or intermittent inotropic therapy acting through β-receptor agonism.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution in the following circumstances:

Bronchospastic disease

In general, patients with bronchospastic disease should not be given beta-blockers of any type (e.g. selective or nonselective), including metoprolol. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered. However, because of its relative cardioselectivity, oral metoprolol may be administered with caution to patients with mild or moderate bronchospastic diseases who do not response 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 metoprolol should be used.

Cardiac failure

β-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency, or unsuspected cardiomyopathy. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure are present, the patient should be fully digitalised and/or given a diuretic and carefully monitored. If cardiac failure develops metoprolol should be discontinued gradually (see *section 4.4 Special warnings and precautions for use – Abrupt withdrawal*). β-blockers should not be used in patients with uncontrolled congestive heart failure; this condition should first be stabilised.

Because of their negative effect on atrioventricular conduction, beta-blockers, including metoprolol, should be given only with caution with first degree atrioventricular block (see *section 4.3 Contraindications*).

Note. Although congestive heart failure has been considered to be a contraindication to the use of β-blockers, there is growing literature on the experimental use of β-adrenergic blocking medicines in heart failure. As further

trials are needed to identify which patients are most likely to respond to which medicines, β-blockers including metoprolol should not normally be prescribed for heart failure outside specialist centres.

Myocardial infarction

In patients with myocardial infarction, if significant hypotension occurs, metoprolol 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.

Abrupt withdrawal

Care should be taken if β-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of β-blockade in patients with ischaemic heart disease. Therefore, it is recommended that the dosage be reduced gradually over a period of 8 to 14 days, during which time the patient's progress should be assessed. Metoprolol should be temporarily reinstituted if the angina worsens markedly or if acute coronary insufficiency develops. If the medicine must be withdrawn abruptly in these patients, close observation is required. In the perioperative period, metoprolol should not be withdrawn unless withdrawal is specifically indicated.

Effects on the heart rate

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/minute) the dosage of metoprolol should be gradually reduced or treatment gradually withdrawn (see *section 4.3 Contraindications*).

Peripheral circulation

β-Blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see *section 4.3 Contraindications*). Metoprolol should be used with caution in patients with peripheral arterial circulatory disorders (for example, Raynaud's disease or phenomenon, intermittent claudication).

Prinzmetal angina

There is a risk of exacerbating the number and duration of coronary artery spasms if patients with Prinzmetal angina or variant angina pectoris are treated with a β-blocker including metoprolol. If this treatment is essential, it should only be undertaken in a coronary or intensive care unit.

Diabetes

Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetes patients should be warned that β-Blockers including metoprolol affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia. In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted. Diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.

Other metabolic effects

β-Adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some medicines affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for medicines with intrinsic sympathomimetic activity.

Phaeochromocytoma

In patients with this condition, or suspected of having this condition an β-blocking medicine (e.g. phentolamine or phenoxybenzamine) should be administered before the β-blocker to avoid exacerbation of hypertension.

Eye and skin reactions

Various rashes and conjunctival xerosis have been reported with β-blocking agents. Cross reactions may occur between β-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

During long-term treatment with the β-blocking medicine practolol a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous or practolol syndrome. On a few rare occasions, serious otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported as part of this syndrome.

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

More recently, an association between Peyronie's disease (a fibrosing induration of the penis) and various β-blockers has been suggested but is not proven.

Allergic conditions

Allergic reactions may be exaggerated by β-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). β-blockers including metoprolol should be avoided if there is a risk of bronchospasm.

In patients taking β-blockers including metoprolol, anaphylactic shock assumes a more severe form and may be resistant to normal doses of adrenaline. Whenever possible, β-blockers including metoprolol should be avoided in patients who are at increased risk of anaphylaxis.

Hyperthyroidism

Special care should be exercised in those patients who are hyperthyroid and also receiving beta-blockers because β-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid status, special care should be exercised in hyperthyroid patients who are also receiving β-blockers. Where metoprolol is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

Interactions

Calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation (see *section 4.5 Interactions with other medicines and other forms of interactions*).

Euthyroid hyperthyroxinaemia

The effects of β-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Conduction disorders

Very rarely, a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). Metoprolol should be administered with caution to patients with first degree A-V block (see *section 4.3 Contraindications*).

Women of child-bearing potential

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

Use in renal impairment

In patients with severe renal disease, haemodynamic changes following β-blockade may impair renal function further. β-blockers, which are excreted mainly by the kidney, may require dose adjustment in patients with renal failure.

Use in hepatic impairment

Metoprolol is mainly eliminated by means of hepatic metabolism (see *section 5.2 Pharmacokinetic Properties*). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Metoprolol blood levels are likely to increase substantially

in patients with hepatic impairment. The elimination half-life of metoprolol is considerably prolonged, depending on severity, in patients with liver impairment. Therefore, metoprolol should be initiated at low doses with cautious gradual dose titration according to clinical response.

Use in the elderly

Caution is indicated in elderly patients. An excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Paediatric use

The safety and efficacy of metoprolol in children have not been established.

Effects on laboratory tests

See *section 4.8 Adverse effects (Undesirable effects)*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on metoprolol

The effects of metoprolol 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.

Concomitant therapy with calcium antagonists

The concomitant use of calcium antagonists with myocardial suppressant and sinus node activity (e.g. verapamil and to a lessor extent diltiazem) and β-blockers may cause bradycardia, hypotension and asystole. Extreme caution is required if these medicines have to be used together. A calcium channel blocker of the phenylalkylamine type (i.e. verapamil) should not be administered intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation. 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 blocker of this type in combination with metoprolol should be closely monitored. The combination of β-blockers with dihydropyridine calcium channel blockers with a weak myocardial depressant effect (e.g. felodipine, nifedipine) can be administered together with caution. In case excess hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

When metoprolol is given together with calcium antagonists of the verapamil and diltiazem type the patient should be monitored for possible negative inotropic and chronotropic effects. Calcium antagonists of the verapamil type should not be given by intravenous administration to patients treated with β-blockers.

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 metaboliser. 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 and medications for stomach ulcers such as cimetidine.

Hydralazine

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

Antiarrhythmic medicines

Care should be taken when prescribing β-blockers with antiarrhythmic medicines. Interactions have been reported during concomitant β-blocker therapy with the class IA agents disopyramide, procainamide, ajmaline and less frequently quinidine; class IB agents, tocainide, mexiletine and lignocaine; class IC agents, flecainide and

propafenone (not available in Australia); the class III agent, amiodarone; and the class IV antiarrhythmic agents (e.g. verapamil). 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.

When metoprolol is given together with antiarrhythmic agents the patient should be monitored for possible negative inotropic and chronotropic effects. The negative inotropic and negative chronotropic effects of antiarrhythmic agents of the quinidine type and amiodarone may be enhanced by β-blockers.

Anaesthesia and the perioperative period

The necessity or desirability of withdrawing beta-blocking agents prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anaesthesia and surgical procedures. The benefits of continuing a treatment with a beta-blocker should be balanced against the risk of withdrawing it in each patient.

β-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance β-blockade be continued perioperatively. The anaesthetist must be made aware of β-blockade because of the potential for interactions with other medicines, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported.

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.

Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of β-blockade. If it is thought necessary to withdraw β-blocker therapy before surgery, this should be done gradually and be completed about 48 hours before surgery (see *section 4.4 Special warnings and precautions for use – Abrupt withdrawal*).

Glyceryl Trinitrate

Glyceryl Trinitrate may enhance the hypotensive effect of metoprolol.

Hepatic enzyme inhibitors

Enzyme-inhibiting substances may exert an influence on the plasma concentration of metoprolol. The plasma concentration of metoprolol may be raised by cimetidine.

Non-steroidal anti-inflammatory drugs

Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker such as indomethacin 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.

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.

Effect of metoprolol on other medicines

Use of catecholamine depleting agents.

Concomitant use of medicines such as reserpine and guanethidine requires careful monitoring since the added effect of a β-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

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. Concurrent use of β-blockers and clonidine should be avoided because of the risk of adverse interaction and severe symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the β-blocker. The rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a beta-blocker. If both drugs are withdrawn simultaneously, a marked rise in blood pressure and/or arrhythmias may result.

Other anti-hypertensive agents

Metoprolol enhances the effects of other antihypertensive medicines. The combined effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive.

Particular care is required when initiating administration of a β-blocker and prazosin together.

Sympathetic ganglion blocking agents, other β-blockers or monoamine oxidase (MAO) inhibitors

Concomitant administration of sympathomimetic such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including, in antitussives or nose and eye drops) may provoke hypertensive reactions when used concomitantly with β-blockers; however, this is less likely with therapeutic doses of β1-selective drugs than with non-selective β-blockers.

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β-blockers (including eye drops), or monoamine oxidase (MAO) inhibitors should be kept under close surveillance.

Prostaglandin synthetase inhibiting agents

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of β-blockers.

Alcohol

Metoprolol may modify the pharmacokinetic behaviour of alcohol when taken together. The plasma level of metoprolol may be raised by alcohol.

Liver enzyme effects

Enzyme-inducing and enzyme-inhibiting substances may change the plasma level of metoprolol. The plasma level of metoprolol is lowered by rifampicin and may be raised by cimetidine, alcohol, hydralazine and selective serotonin re-uptake inhibitors (SSRIs), e.g. paroxetine, fluoxetine and sertraline.

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. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a beta1-selective drug such as metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained (see *section 4.4 Special warnings and precautions for use*).

Anaesthetics

Inhalation anaesthetics enhance the cardiosuppressant effect of beta-blocker therapy (see *section 4.4 Special warnings and precautions for use*). Metoprolol may also reduce the clearance of other drugs (e.g. lignocaine, leading to increased lignocaine effects).

Warfarin

A limited number of reports have demonstrated a rise in AUC and concentration of warfarin when taken with another β-blocker. This could potentially increase the anti-coagulant effect of warfarin.

Digitalis glycosides

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

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category C

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.

β-blockers may cause pharmacological effects such as bradycardia in the foetus and newborn infant. Experience with metoprolol in the first trimester of pregnancy is limited, but no foetal malformations attributable to metoprolol have been reported. However, beta-blockers may reduce placental perfusion and clinical experience suggests that in cases where its use is considered to be essential, metoprolol may be administered during pregnancy.

During the later stages of pregnancy these medicines should only be given after weighing the needs of the mother against the risk to the foetus.

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 β-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Animal studies have not demonstrated adverse maternal or foetal effects except in high doses in the rabbit, where slight reduction of litter size and slightly higher value of foetal loss were demonstrated.

There are few clinical data on the use of metoprolol tartrate during the first trimester of pregnancy.

Metoprolol crosses the placental barrier in pregnant women; in one study the concentration in the umbilical vein was almost the same as in maternal vein plasma.

Use in lactation

Metoprolol is excreted in human breast milk. β-blockers taken by the mother may cause side effects, e.g. bradycardia, in the breastfed infant, although when the doses used are within the recommended therapeutic range, the very small amount of the drug ingested by the infant renders such effects unlikely. Experience suggests that metoprolol only need be discontinued during lactation if the infant's hepatic function is severely impaired.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Metoprolol may cause dizziness, fatigue or visual disturbances (see *section 4.8 Adverse effects (Undesirable effects)*) and, therefore, may adversely affect the patient's ability to drive or use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 1: Cardiovascular adverse effects (related, possibly related, unassessable or unknown) reported by ≥1% in 1,395 patients during randomised clinical trials of metoprolol and placebo:

	Metoprolol	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

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).

Table 2: Adverse drug reactions from clinical trials

Blood and the lymphatic system disorders	
Rare	agranulocytosis
Very rare	thrombocytopenia
Psychiatric disorders	
Rare	depression, nightmares
Very rare	personality disorder, hallucinations, mental confusion
Nervous system disorders	
Common	dizziness, headache
Rare	depressed level of consciousness, somnolence or insomnia, paraesthesia, short term memory loss
Eye disorders	
Very rare	visual impairment (e.g. blurred vision), dry eyes, eye irritation
Ear and labyrinth disorders	
Very rare	tinnitus, hearing disorders[1] (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	bradycardia
Rare	cardiac failure, arrhythmias, palpitation
Very rare	conduction disorders, precordial pain
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope), peripheral oedema, hypertension (mild and transient), cold extremities, arterial insufficiency
Rare	oedema, Raynaud's phenomenon
Very rare	Gangrene[2], angina (mild and transient), intermittent claudication
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, exertional dyspnoea
Rare	Bronchospasm[3]
Very rare	rhinitis
Gastrointestinal disorders	
Common	nausea and vomiting, abdominal pain, heartburn, flatulence, gastric pain
Rare	diarrhoea or constipation
Very rare	dry mouth, retroperitoneal fibrosis (relationship to metoprolol has not been definitely established), unstable diabetes
Hepatobiliary disorders	
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Common	pruritis, rash
Rare	rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	Photosensitivity reaction, hyperhydrosis, reversible alopecia, worsening of psoriasis, sweating increased
Musculoskeletal, connective tissue disorders	
Rare	muscle spasms
Very rare	arthritis, musculoskeletal pain
Reproductive system and breast disorders	
Very rare	erectile dysfunction, libido disorder and potency, Peyronie's disease[4]

Immune system disorders	
	hypersensitivity
General disorders and administration site conditions	
Common	fatigue, tiredness
Investigations	
Very rare	weight gain, liver function test abnormal

[1] 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 metoprolol has not been definitely established

Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta-blocker, practolol, has not been reported with metoprolol (see *section 4.4 Special warnings and precautions for use*).

Postmarketing Data

In addition to the adverse events reported in the clinical trials, the following events have been reported during post-marketing surveillance of metoprolol*:

Nervous system disorders:
Confusional state

Psychiatric disorders:
Increase in blood triglycerides, decrease in high density lipoprotein (HDL)

** Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.*

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol.

Cardiac disorders	intensification of AV block (see *section 4.3 Contraindications*)
Blood and the lymphatic system disorders	nonthrombocytopenic purpura, thrombocytopenic purpura
Nervous system disorders	reversible mental depression progressing to catatonia, an acute reversible syndrome characterised by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance in neuropsychometrics
Hypersensitivity reactions	fever combined with aching and sore throat, laryngospasm, and respiratory distress

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Symptoms: Overdosage is characterised by excessive bradycardia, hypotension, possible cardiac failure and bronchoconstriction. AV block, cardiogenic shock, impairment of consciousness (even coma), convulsions, nausea, vomiting and cyanosis may also occur. Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first signs of overdose can appear in 20 minutes after ingestion of tablets, but are more commonly seen within one to two hours. The effects of massive overdosage may persist for several days despite declining plasma concentrations.

Treatment: Noumed Metoprolol should be withdrawn. The patient should be hospitalised 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 general, patients with acute or recent myocardial infarction may be more haemodynamically unstable than other patients and should be treated accordingly.

In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage (if within 4 hours after ingestion of metoprolol) and/or activation 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-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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Metoprolol tartrate is structurally related to other cardioselective β-blockers. It is a relatively cardioselective β-adrenoceptor blocking medicine without intrinsic sympathomimetic activity, and is suited for the treatment of hypertension. It acts on β1-receptors mainly located in the heart at lower doses than those needed to influence the β2-receptors mainly located in the bronchi and peripheral vessels. Metoprolol reduces blood pressure in patients with hypertension, in both the standing and supine position. It also reduces the extent of rises in blood pressure occurring in response to physical and mental stress. In angina pectoris metoprolol reduces the frequency and severity of the attacks and the need for glyceryl trinitrate relief, and increases exercise tolerance.

Metoprolol has been shown to reduce mortality in patients with suspected or definite myocardial infarction. The mechanisms of action for these effects are not fully understood but may be related to a lower incidence of ventricular fibrillation and limitation of infarct size. Metoprolol has also been shown to reduce the incidence of recurrent myocardial infarction.

In cases of supraventricular tachycardia or atrial fibrillation, and in the presence of extra systoles, metoprolol has a regulating effect on the heart rate.

Orthostatic effects or disturbances of electrolyte balance have not been observed.

In therapeutic doses, metoprolol has less effect on the peripheral circulation and the bronchial muscles than non-selective β-blockers. However, metoprolol should be used with caution in patients with asthma, and concomitant use of an adrenergic bronchodilator, e.g. terbutaline or salbutamol, is advisable. Patients with reversible airways obstruction who are already taking β2-stimulants may require adjustment of the dosage of these if metoprolol therapy is subsequently introduced.

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 will inhibit catecholamine induced lipolysis. It has also been shown to reduce diuretic induced increases in plasma renin activity. Metoprolol will inhibit catecholamine induced insulin secretion to a far lesser degree than non-selective β-blockers.

Metoprolol is practically devoid of membrane stabilising activity and does not display partial agonist activity (i.e. intrinsic sympathomimetic activity = ISA) at doses required to produce β-blockade.

Metoprolol tartrate forms an active metabolite which does not, however, contribute significantly to the therapeutic effect.

Metoprolol is considered a relatively lipid soluble compound, i.e. less soluble than propranolol and more lipid soluble than atenolol. It has been shown to exert a prophylactic effect in both classical and common migraine.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Metoprolol is rapidly and almost completely (more than 95%) absorbed from the gastrointestinal tract.

Distribution

It is rapidly and extensively distributed to the extravascular tissues. The volume of distribution is 5.6L/kg. At therapeutic concentrations, approximately 12% is bound to human serum proteins.

Metabolism

Long-term studies have shown that metoprolol neither enhances nor inhibits its own metabolism.

The elimination half-life of metoprolol tartrate is between three and five hours. The duration of the β-blocking effect is dose dependent (as measured by reduction of exercise heart rate).

Excretion

Studies with the radioactively labelled drug have shown that more than 90% of the dose is excreted in the urine within 72 hours, mainly in the form of known metabolites. Only about 3% of the administered dose is excreted unchanged in the urine in 72 hours. The rate of renal excretion of metoprolol has a linear relationship to its plasma concentration. Metoprolol is excreted mainly by glomerular filtration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, hyprolose, calcium hydrogen phosphate dihydrate and crospovidone.

6.2 INCOMPATIBILITIES

Refer to *section 4.5 – Interactions with other medicines and other forms of interactions*.

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Noumed Metoprolol 50mg Tablets: PVC/PVDC Aluminium blister packs of 100 tablets

Noumed Metoprolol 100mg Tablets: PVC/PVDC Aluminium blister packs of 60 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

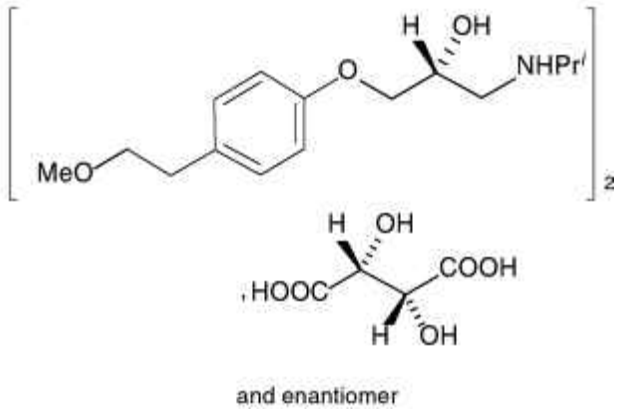
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: di[(*RS*)-3-[4-(2-methoxyethyl)phenoxy]-1-(isopropylamino)propan-2-ol] tartrate

Metoprolol tartrate is a white crystalline powder. Melting point: approximately 120°C. The powder is practically odourless. It is very soluble in water, soluble in chloroform, methylene chloride and alcohol, and almost insoluble in benzene, diethyl ether and acetone.

Chemical structure:



and enantiomer

$(C_{15}H_{25}NO_3)_2 . C_4H_6O_6$ MW = 684.8

CAS number:

56392-17-7

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd

Level 5, 7 Eden Park Drive,

Macquarie Park, NSW 2113

Phone: 1800 930 999

9. DATE OF FIRST APPROVAL

26 February 2018

10. DATE OF REVISION

05 March 2021

Summary table of changes

Section changed	Summary of new information
2	Minor editorial update – relocate excipient information to section 6.1.
4.3	Safety related update to strengthen warning regarding: Bronchial asthma/bronchospasm; and Hypersensitivity to metoprolol tartrate related derivatives.
4.4	Safety related update to strengthen warning regarding: Abrupt withdrawal; Eye and skin reactions; and Use in hepatic impairment.
4.5	Safety related update to add or strengthen interactions regarding: Non-steroidal anti-inflammatory drugs; Other drugs causing decrease in heart rate (e.g. fingolimod); Other drugs causing decrease in blood pressure (e.g. aldesleukin); Other anti-hypertensive agents; Sympathetic ganglion blocking agents, other β-blockers or monoamine oxidase (MAO) inhibitors; Anaesthetics; and Digitalis glycosides.
4.8	Minor editorial correction to table 2.
6.1, 6.5	Minor editorial update.
8	Corrected Sponsor's address. Removed distributor's details.