

METOPROLOL IV MYLAN



1. Product Name

Metoprolol IV Mylan, 5 mg/5 mL, solution for injection

2. Qualitative and Quantitative Composition

Each vial contains 5 mg metoprolol tartrate.

Each mL contains 1 mg metoprolol tartrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Metoprolol IV Mylan is a clear, colourless solution for injection, available as 5 mg/5 mL in clear glass vials.

4. Clinical Particulars

4.1 *Therapeutic indications*

Adults

Disturbances of cardiac rhythm, including supraventricular and ventricular arrhythmias.

4.2 *Dose and method of administration*

Parenteral administration of metoprolol should be supervised by experienced staff in a setting in which monitoring and resuscitating equipment are available.

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

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.

Special populations

Paediatric

The safety and efficacy of metoprolol tartrate in paediatric patients has not been established.

Hepatic impairment

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

Elderly (> 65 years)

No dose adjustment of metoprolol tartrate is required in elderly 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 listed in section 6.1; hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur)
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- Right ventricular failure secondary to pulmonary hypertension
- Significant right ventricular hypertrophy
- Atrioventricular block of second or third degree
- Decompensated heart failure (see section 4.4)
- Sinus bradycardia (heart rate less than 45 to 50 beats/min)
- Sick-sinus syndrome
- Severe peripheral arterial circulatory disorders
- Shock (including cardiogenic shock and hypovolaemic shock)
- Untreated pheochromocytoma (see section 4.4)
- Hypotension
- Use of metoprolol tartrate 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 moderate to severe heart failure.
- Continuous or intermittent inotropic therapy acting through beta-receptor agonism
- Bronchial asthma, bronchospasm and/or history of bronchospasm

Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

Therefore, beta-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardio selective beta blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

4.4 Special warnings and precautions for use

Blood pressure and ECG should be monitored during the treatment.

Product is for single use in one patient only.

Bronchospastic diseases

In general, patients with bronchospastic diseases should not be given beta-blockers, including metoprolol tartrate. However, because of its relative cardioselectivity, oral metoprolol tartrate 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 beta₁-selectivity is not absolute, a beta₂-agonist should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used.

Diabetic patients

Metoprolol tartrate should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents (see section 4.5). Diabetic patients should

be warned that beta-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia; however, other manifestations of hypoglycaemia such as dizziness and sweating may not be significantly suppressed, and sweating may be increased.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, beta-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 tartrate should be monitored to ensure diabetes control is maintained.

Cardiovascular system

Beta-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 persists, metoprolol tartrate should be discontinued gradually (see section 4.4).

Beta-blockers, including metoprolol tartrate, should not be used in patients with untreated congestive heart failure (see section 4.3). This condition should first be stabilised.

(Note: Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is growing literature on the experimental use of beta-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, beta-blockers should not normally be prescribed for heart failure outside specialist centres.)

Conduction disorders

Very rarely a pre-existing atrioventricular conduction disorder of moderate degree may become aggravated (possibly leading to atrioventricular block). METOPROLOL IV MYLAN should be administered with caution to patients with first degree atrioventricular block (see section 4.3).

Effects on the heart rate

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).

Myocardial infarction

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

Metoprolol tartrate 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 impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see section 4.3).

Pheochromocytoma

In patients with this condition, an alpha-blocking drug (e.g. phentolamine/phenoxybenzamine) should be administered before the beta-blocker to avoid exacerbation of hypertension (see section 4.3).

General anaesthesia Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs, 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 tartrate 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 beta-blockade. If it is thought necessary to withdraw beta-blocker, including metoprolol tartrate, therapy before surgery, this should be done gradually and completed about 48 hours before surgery (see section 4.4).

Abrupt withdrawal

Care should be taken if beta-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 beta-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 tartrate should be temporarily reinstated if the angina worsens.

If the drug must be withdrawn abruptly in these patients, close observation is required. In the peri-operative period metoprolol tartrate should not be withdrawn, unless withdrawal is specifically indicated.

Allergic conditions

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

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

Prinzmetal's angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a beta-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Hyperthyroidism

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

Effects on the eye and skin

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

During long-term treatment with the beta-blocking drug practolol a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of the 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 and pleurisy have been reported as part of this syndrome.

The oculomucocutaneous syndrome as reported with practolol has not been reported with metoprolol tartrate. However, dry eyes and skin rashes have been reported with metoprolol tartrate. In most cases the symptoms cleared when metoprolol tartrate treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such symptoms occur, discontinuation of metoprolol tartrate should be considered.

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

Intravenous therapy

The intravenous administration of metoprolol tartrate to patients with a systolic blood pressure below 100 mmHg (13.3 kPa) should be carried out with special care as it can result in a further significant decrease of blood pressure.

Concomitant therapy with calcium antagonists

The concomitant use of calcium antagonists with myocardial suppressant and sinus node activity (e.g. verapamil and to a lesser extent diltiazem) and beta-blockers may cause bradycardia, hypotension and asystole. Extreme caution is required if these drugs have to be used together.

A calcium antagonist of the phenylalkylamine type (e.g. verapamil) should not be administered intravenously to patients receiving metoprolol tartrate because there is a risk of cardiac arrest in this situation (see section 4.5). Patients taking oral calcium antagonists of this type in combination with metoprolol tartrate should be closely monitored.

The combination of beta-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.

Clonidine

Concurrent use of beta-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker.

Antiarrhythmic drugs

Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone; the Class III agent, amiodarone; and the Class IV antiarrhythmic agents (e.g. verapamil).

Catecholamine depleting agents

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

Effects on the thyroid

The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T₄) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Other metabolic effects

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

Special populations

Hepatic impairment

Metoprolol is mainly eliminated by means of hepatic metabolism (see section 5.2). Therefore, liver cirrhosis may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma levels.

Renal impairment

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

Elderly 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.

See section 5.2.

Paediatric

The safety and efficacy of metoprolol tartrate in paediatric patients has not been established.

4.5 Interaction with other medicines and other forms of interaction

Calcium channel blockers

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 oral calcium channel blockers of the verapamil or diltiazem type in combination with metoprolol tartrate should be closely monitored.

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 metoprolol tartrate because there is a risk of cardiac arrest in this situation (see section 4.4).

Other anti-hypertensive agents

Metoprolol enhances the effects of other antihypertensive drugs.

Catecholamine depleting drugs, sympathetic ganglion blocking agents, other beta-blockers or monoamine oxidase (MAO) inhibitors

Patients receiving concurrent treatment with catecholamine depleting drugs, sympathetic ganglion blocking agents, other beta-blockers (including those in form of eye drops, such as timolol), or monoamine oxidase (MAO) inhibitors, should be under close surveillance. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

Anti-arrhythmic agents

When metoprolol tartrate is given together with anti-arrhythmic agents the patient should be monitored for possible negative inotropic and chronotropic effects. Beta-blockers may potentiate the negative inotropic and chronotropic effects 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 metoprolol tartrate on heart rate and atrioventricular conduction.

Warfarin

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

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of metoprolol tartrate.

Anaesthetics

Inhalation anaesthetics enhance the cardiosuppressant effect of beta-blocker therapy (see section 4.4). Metoprolol may also reduce the clearance of other drugs (e.g. lignocaine).

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). 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 pre-systemic metabolism of metoprolol leading to increased concentrations of metoprolol.

Digitalis glycosides

Digitalis glycosides, in association with beta blockers, may increase atrioventricular conduction time and may induce bradycardia. 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 beta₁-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.

Prostaglandin synthetase inhibiting agents

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

Hepatic enzyme inducers

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

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 concomitant treatment with clonidine is to be discontinued, the beta-blocker medication should be withdrawn several days before clonidine. 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.

Antidiabetic agents and insulin

Beta-blockers may interfere with the usual hemodynamic response to hypoglycaemia 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 beta₁-selective drug such as metoprolol tartrate than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol tartrate should be monitored to ensure that diabetes control is maintained. The dosages of oral antidiabetics may need to be adjusted in patients receiving beta-blockers. See section 4.4.

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 metoprolol tartrate. Particular care is required when initiating administration of a beta-blocker and prazosin together.

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 when taken together. The plasma level of metoprolol may be raised by alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

In general, no drug should be taken during the first 3 months of pregnancy, and drugs should only be given after weighing the needs of the mother against the risk to the foetus throughout pregnancy.

Metoprolol should not be given during pregnancy unless its use is considered essential. In general, β -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. Beta-blockers may cause bradycardia in the foetus and new-born infant.

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. The lowest possible dose should be used and discontinuation of treatment should be considered at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Breast-feeding

Metoprolol is excreted in human breast milk. Beta-blockers taken by the mother may cause side-effects, e.g. bradycardia, in the breast fed infant, although when the doses used are within the recommended therapeutic range, the very small amount of drug ingested by the infant (with therapeutic doses, an infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of metoprolol) renders such effects unlikely.

Experience suggests that metoprolol tartrate only need be discontinued during lactation if the infant's hepatic function is severely impaired. Nevertheless, breast-fed infants should be closely observed for signs of beta-blockade.

Fertility

For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Occasionally, especially at the start of treatment, beta blockers may give rise to gastro-intestinal upsets, sleep disturbances, or exertional tiredness. These effects, however, are of a mild nature and seldom necessitate a reduction in the dosage.

The following events have been reported as adverse events in clinical trials or reported from routine use. In many cases a relationship with metoprolol has not been established. The

following definitions of frequency are used: very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($<1/10,000$).

Blood and the lymphatic system disorders	
Very rare	thrombocytopenia
Psychiatric disorders	
Uncommon	depression, impaired concentration, somnolence or insomnia, nightmares
Rare	nervousness, anxiety
Very rare	personality disorder, hallucinations, amnesia/memory impairment, confusion
Nervous system disorders	
Very common	fatigue
Common	dizziness, headache
Uncommon	paraesthesia, muscle cramps
Rare	depressed level of consciousness,
Sense disorders	
Rare	disturbances of vision (e.g. blurred vision), dry eyes, irritated eyes, conjunctivitis (see section 4.4)
Very rare	tinnitus ¹ , hearing disorders (e.g. hypoacusis or deafness), taste disturbances
Cardiovascular disorders	
Common	Bradycardia, orthostatic hypotension (occasionally with syncope), postural disorders (very rarely with syncope), cold hands and feet (Raynaud's phenomenon), palpitations, clinically significant falls in blood pressure after intravenous administration
Uncommon	transient deterioration of heart failure symptoms, A-V block I, oedema, precordial pain, cardiogenic shock in patients with acute myocardial infarction ² .
Rare	cardiac arrhythmias, disturbances of cardiac conduction
Very rare	gangrene ³
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea on exertion
Uncommon	bronchospasm ⁴
Rare	rhinitis
Gastrointestinal disorders	
Common	nausea, vomiting, abdominal pain, diarrhea, constipation
Rare	dry mouth
Very rare	retroperitoneal fibrosis ⁵
Hepatobiliary disorders	
Rare	liver function test abnormalities
Very rare	hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), increased sweating
Rare	Loss of hair
Very rare	photosensitivity reaction, aggravated psoriasis
Musculoskeletal, connective tissue disorders	
Rare	muscle spasms
Very rare	arthritis

¹ and, in doses exceeding those recommended

² excess frequency of 0.4% compared with placebo in a study of 46000 patients with acute myocardial infarction where the frequency of cardiogenic shock was 2.3% in the metoprolol group and 1.9% in the placebo group in the subset of patients with low shock risk index. The shock risk index was based on the absolute risk of shock in each individual patient derived from age, sex, time delay, Killip class, blood pressure, heart rate, ECG abnormality, and prior history of hypertension. The patient group with low shock risk index corresponds to the patients in which metoprolol is recommended for use in acute myocardial infarction.

³ in patients with pre-existing severe peripheral circulatory disorders

⁴ which may occur in patients without a history of obstructive lung disease

⁵ relationship to metoprolol has not been definitely established

Reproductive system and breast disorders	
Rare	impotence/sexual dysfunction
Very rare	erectile dysfunction, libido disorder, Peyronie's disease ⁶
Metabolism and nutrition disorders	
Uncommon	weight gain
Miscellaneous	
Very rare	arthralgia

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

The following adverse reactions have been derived from post-marketing experience with metoprolol tartrate 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.

Investigations

Blood triglycerides increased, High Density Lipoprotein (HDL) decreased.

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, sinus bradycardia and bradyarrhythmia, cardiac conduction disturbances, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting and cyanosis. The main clinical signs of overdosage are cardiovascular and in some cases decompensation may be rapid. Overdosage with metoprolol can lead to death.

Cases of overdosage in paediatric patients need to be given extra attention even if the patient appears well on presentation.

Management

Care should be provided at a facility that can provide appropriate supporting measures, monitoring, and supervision. 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.

Atropine, adreno stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

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.

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

⁶ relationship to metoprolol has not been definitely established

administration of adreno stimulating drugs such as dobutamine, with α_1 receptor agonistic drugs added in presence of vasodilation. Intravenous use of calcium salts (Ca^{2+}) can also be considered.

Dopamine, dobutamine or noradrenaline may be given to maintain blood pressure.

Diazepam is the drug of choice for controlling seizures.

Bronchospasm can usually be reversed by bronchodilators; 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) may occur after overdose.

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardioselective beta-blocker

ATC code: C07A B02.

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

Metoprolol is an aryloxypropanolamine derivative.

Mechanism of action

Metoprolol is a relatively cardioselective beta adrenoceptor blocking drug without intrinsic sympathomimetic activity, and is suited for the treatment of hypertension. It acts on β_{1} -receptors mainly located in the heart at lower doses than those needed to influence the β_{2} -receptors mainly located in the bronchi and peripheral vessels.

Pharmacodynamic effects

Metoprolol tartrate reduces the 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. 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 in blood pressure seen with metoprolol appears to parallel this gradual decrease in total peripheral resistance.

In angina pectoris metoprolol reduces the frequency and severity of the attacks and the need for glyceryl trinitrate relief, and increases exercise tolerance. These beneficial effects may be due to decreased myocardial oxygen demand as a result of the reduced heart rate and myocardial contractility.

Metoprolol has been shown to reduce mortality in patients with suspected or definite myocardial infarction. The mechanisms of action for these effects of metoprolol 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 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.

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

In therapeutic doses, metoprolol tartrate has less effect on the peripheral circulation and the bronchial muscles than non selective beta-blockers. However, metoprolol tartrate 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 beta-2 stimulants may require adjustment of the dosage of these if metoprolol tartrate 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 tartrate will inhibit catecholamine-induced lipolysis.

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

Metoprolol tartrate 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 beta-blockade.

Metoprolol tartrate forms an active metabolite (2-hydroxymetoprolol), which does not, however, contribute significantly to the therapeutic effect.

Metoprolol tartrate is considered a relatively lipid-soluble compound i.e. less soluble than propranolol and more lipid soluble than atenolol.

Metoprolol has been shown to exert a prophylactic effect in both classical and common migraine.

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 beta₁-adrenoreceptor antagonistic activity is essential for minimum pharmacodynamic effect which is observed with about 45 nanomol/L metoprolol in plasma.

5.2 Pharmacokinetic properties

Absorption

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 to the extravascular tissues. The volume of distribution is 5.6 L/kg. At therapeutic concentrations, approximately 12% of metoprolol tartrate is bound to human serum proteins

Biotransformation

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

Elimination

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 tartrate has a linear relationship to its plasma concentration. Metoprolol tartrate is excreted mainly by glomerular filtration.

The elimination half-life of metoprolol tartrate is between 3 and 5 hours.

Dose response

The duration of the beta-blocking effect is dose dependent (as measured by reduction of exercise heart rate). For instance, in healthy subjects the effect of 20 mg metoprolol tartrate given intravenously is halved after about 6 hours.

Special population

Elderly patients

Elderly subjects showed no significant differences in the plasma concentrations of metoprolol as compared with young subjects, in a study involving eight healthy elderly (mean age 74.5 years) and eight healthy young (mean age 26.3 years) subjects.

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 hyperthyroidism

Hyperthyroidism may increase the pre-systemic 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*

Metoprolol IV Mylan also contains

- sodium chloride and
- water for injections.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

2 years.

6.4 *Special precautions for storage*

Store below 25°C. Protect from light.

6.5 *Nature and contents of container*

Carton of 5 glass vials.

6.6 *Special precautions for disposal*

No special requirements for disposal.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
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AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

28 February 2018

10. Date of Revision of the Text

8 April 2020

Summary table of changes

Section	Summary of new information
-	Editorial updates
4.3	Added contraindications: allergic disorders, right ventricular failure and hypertrophy, inotropic therapy, bronchospasm
4.4	Added warnings: monitoring during treatment, single use product, intravenous therapy, clonidine, antiarrhythmic drugs, catecholamine depleting agents, thyroid, metabolic effects, renal impairment Amended warnings: diabetic patients, cardiovascular system, conduction disorders, pheochromocytoma, anaesthesia, withdrawal, allergic conditions, Prinzmetal's angina, hyperthyroidism, effects on eyes and skin, calcium antagonists
4.5	Added interactions: sympathetic ganglion blocking agents, warfarin, prostaglandin synthetase inhibiting agents, clonidine Amended warnings: anaesthetics, hepatic enzyme inducers
4.6	Amended information regarding use in pregnancy and lactation
4.8	Added AEs: impaired concentration, somnolence, nervousness, anxiety, impotence, amnesia, confusion, fatigue, paraesthesia, muscle cramps, conjunctivitis, taste disturbance, postural disorders, precordial pain, cardiogenic shock, liver function abnormal, increased sweating, arthralgia
4.9	Added statements regarding: cardiac insufficiency, bradyarrhythmia, cardiac conduction disorders, overdose in children
5.1	Added pharmacodynamic effects
5.2	Updated information on distribution, biotransformation, elimination, dose response and elderly patients