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
No paediatric studies have been performed. 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 geriatric patients but it should be given with
cautious 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 phaeochromocytoma (see section 4.4)
- Hypotension
- Bronchial asthma and history of bronchospasm.

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

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

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 aggravate such conditions (see section 4.3).

**Phaeochromocytoma**

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

**Anaesthesia and surgery**

The necessity, or desirability, of withdrawing beta-blocking agents, including metoprolol tartrate, 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 treatment with a beta-blocker, including metoprolol tartrate, should be balanced against the risk of withdrawing it in each patient. If a patient treated with metoprolol tartrate 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). 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 the general anaesthetic.

**Abrupt withdrawal**

Metoprolol tartrate 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 metoprolol tartrate, 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 beta₁-receptor blockers, such as metoprolol tartrate, 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 metoprolol tartrate 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 metoprolol tartrate. However, part of this syndrome (dry eyes either alone or,
occasionally, with skin rashes) has occurred. In most cases the symptoms cleared when metoprolol tartrate treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol tartrate should be considered.

**Interactions**

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 4.5).

**Special populations**

**Hepatic impairment**

Metoprolol is mainly eliminated by means of hepatic metabolism (see section 5.2). 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 interaction**

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

**Other antihypertensive drugs**

The effects of metoprolol tartrate 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 metoprolol tartrate 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 metoprolol tartrate on heart rate and atrioventricular conduction.

**Nitroglycerin**

Nitroglycerin may enhance the hypotensive effect of metoprolol tartrate.
General anaesthetics
Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers (see section 4.4).

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, arrhythmics 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
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.

Interactions resulting in effects on other drugs

Anti-adrenergic agents
Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpin, alpha-methylpopa 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 metoprolol tartrate concurrently, and clonidine treatment is to be discontinued, metoprolol tartrate should be stopped several days before clonidine is withdrawn.

Antidiabetic drugs 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 (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.

**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

**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 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 foetal malformations attributable to metoprolol have been reported. However, beta-blockers may reduce placental perfusion.

In the case of treatment with metoprolol tartrate 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).

**Breast-feeding**

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.

**Fertility**

For pre-clinical fertility data refer to section 5.3.

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

Dizziness, fatigue or visual impairment may occur during treatment with metoprolol tartrate (see section 4.8), 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, 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 |
| Respiratory, thoracic and mediastinal disorders | Common | exertional dyspnoea |
| | Rare | bronchospasm |
| | Very rare | rhinitis |
| Gastrointestinal disorders | Common | nausea and vomiting, abdominal pain |
| | Rare | diarrhoea or constipation |
| | Very rare | dry mouth, retroperitoneal fibrosis |
| Hepatobiliary disorders | Very rare | hepatitis |
| Skin and subcutaneous tissue disorders | Very rare | rash (in the form of urticaria, psoriasiform and dystrophic skin lesions) |
| | Very rare | photosensitivity reaction, hyperhidrosis, 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 |
| General disorders and administration site conditions | Common | fatigue |
| Investigations | Very rare | weight increase, liver function test abnormalities |

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1. and, in doses exceeding those recommended
2. in patients with pre-existing severe peripheral circulatory disorders
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.

*Nervous system disorders*

Confusional state

*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*

An overdosage of metoprolol tartrate 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, 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 metoprolol tartrate. 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.

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 beta₂-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) 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 cardioselective beta-blocker; it blocks beta\textsubscript{1}-adrenergic receptors (which are mainly located in the heart) at lower doses than those needed to block beta\textsubscript{2}-receptors, which are mainly located in the bronchi and peripheral vessels. It has no membrane-stabilising effect nor partial agonist (intrinsic sympathomimetic) activity.

Pharmacodynamic effects
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 in 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.

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 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, 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). In patients with hypertension, metoprolol concentrations in cerebrospinal fluid are similar to those in plasma. Metoprolol is not a significant P-glycoprotein substrate indicating that inter-individual variability in pharmacokinetics of metoprolol can be majorly due to CYP2D6 metabolism.

Biotransformation
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. In most subjects (extensive metabolisers), less than 10% of an intravenous dose, is excreted as unchanged drug. In poor metabolisers, up to 30% or 40% of an intravenous dose may be excreted unchanged. The total plasma clearance of metoprolol after intravenous administration is approximately 1 L/min.

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 patients 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 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.

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**7. Medicines Schedule**

Prescription Medicine

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**8. Sponsor Details**

Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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**9. Date of First Approval**

28 February 2018

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**10. Date of Revision of the Text**

28 February 2018  
Added Adult heading to 4.1.