



APO- METOPROLOL

1. PRODUCT NAME

APO-METOPROLOL (50mg and 100mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50mg tablet contains metoprolol tartrate equivalent to 50mg metoprolol.

Each 100mg tablet contains metoprolol tartrate equivalent to 100mg metoprolol.

Excipient(s) of known effect
APO-METOPROLOL contain lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Apo-Metoprolol 100 mg tablets are white to off white, round, biconvex film-coated tablets with notch break line on one side and '100' debossed on other side.

Apo-Metoprolol 50 mg tablets are pink, round, biconvex film-coated tablets with notch break line on one side and '50' debossed on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Disturbances of cardiac rhythm, including supraventricular and ventricular arrhythmias.

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

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

Hyperthyroidism (as adjunctive medication).

Functional heart disorders with palpitation.

Prevention of migraine.

4.2 Dose and method of administration

For oral treatment, the tablets should be swallowed unchewed.

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

Disturbances of cardiac rhythm

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

Hypertension

The daily oral dose is 100 to 200 mg, given either as a single dose in the morning or as 2 divided doses (morning and evening). If necessary, another antihypertensive can be prescribed in addition (see section 4.1 Therapeutic indications).

Angina pectoris

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

Hyperthyroidism

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

Functional heart disorders with palpitation

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

Prevention of migraine

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

Paediatric patients

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, Apo-Metoprolol should be initiated at low doses with cautious gradual dose titration according to clinical response.

Geriatric patients (>65 years)

No dose adjustment of Apo-Metoprolol is required in geriatric patients but it should be given with caution due to increased likelihood of adverse events.

4.3 Contraindications

Hypersensitivity to metoprolol and related derivatives, or to any of the excipients.

Hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur).

- Atrioventricular block of second or third degree.
- Decompensated heart failure.
- Clinically relevant sinus bradycardia (heart rate less than 45 to 50 beats/min).
- Sick-sinus syndrome.
- Severe peripheral arterial circulatory disorders.
- Cardiogenic shock.

- Untreated phaeochromocytoma (see section 4.4 Special Warnings and Precautions for use).
- Hypotension.

For oral use: severe bronchial asthma or history of severe bronchospasm (see section 4.4 Special Warnings and Precautions for use).

Use of Apo-Metoprolol 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

Bronchospastic diseases

In general, patients with bronchospastic diseases should not be given beta-blockers, including Apo-Metoprolol. However, because of its relative cardioselectivity, oral Apo-Metoprolol 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 beta 2-agonist should be administered concomitantly, and the lowest possible dose of Apo-Metoprolol should be used.

Diabetic patients

Apo-Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents (see 4.5 Interactions with other medicines and other forms of interaction). Diabetic patients should be warned that beta-blockers, including Apo-Metoprolol, 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 Apo-Metoprolol, should not be used in patients with untreated congestive heart failure (see section 4.3 Contraindications). This condition should first be stabilised. Because of their negative effect on atrioventricular conduction, beta-blockers, including Apo-Metoprolol, should be given only with caution to patients with first degree atrioventricular block (see section 4.3 Contraindications).

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

Myocardial infarction

In patients with myocardial infarction, if significant hypotension occurs, Apo-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.

Peripheral circulatory disorders

Apo-Metoprolol should be used with caution in patients with peripheral arterial circulatory disorders (for example, Raynaud's disease or phenomenon, intermittent claudication), because betablocker treatment may aggravate such conditions (see section 4.3 Contraindications).

Pheochromocytoma

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

Anesthesia and surgery

The necessity, or desirability, of withdrawing beta-blocking agents, including Apo-Metoprolol, prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. The benefits of continuing a treatment with a beta-blocker, including Apo-Metoprolol, should be balanced against the risk of withdrawing it in each patient. If a patient treated with Apo-Metoprolol needs general anaesthesia, the anaesthetist should be informed that the patient is receiving a betablocker. An anaesthetic agent with as little cardio depressant effect as possible should be used (see section 4.5 Interactions with other medicines and other forms of interaction). If it is thought necessary to withdraw beta-blocker, including Apo-Metoprolol, therapy before surgery, this should be done gradually and completed about 48 hours before the general anaesthetic.

Abrupt withdrawal

Apo-Metoprolol 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 Apo-Metoprolol, 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 Apo-Metoprolol, 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 Apo-Metoprolol 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 Apo-Metoprolol should be considered.

4.5 Interactions with other medicines and other forms of interaction

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

Hepatic impairment

Metoprolol undergoes substantial hepatic first-pass metabolism, and is mainly eliminated by means of hepatic metabolism (see section 5.2 Clinical pharmacology, Pharmacokinetics Properties). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations.

Geriatric patients

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

Interactions

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 Apo-Metoprolol because there is a risk of cardiac arrest in this situation (see section 4.4 Special Warnings and Precautions for use)

Other antihypertensive drugs

The effects of Apo-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. 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 Apo-Metoprolol 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

electrophysiologic effects including bradycardia, sinus arrest, and atrioventricular block antiarrhythmic agents such as quinidine tocinide, procainamide, ajmaline amiodarone, flecainide and disopyramide may potentiate the effects of Apo-Metoprolol on heart rate and atrioventricular conduction.

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of Apo-Metoprolol.

General anaesthetics

Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers (see section 4.4 Special Warnings and Precautions for use).

CYP2D6 inhibitors

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol tartrate. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer (phenocopying, see Clinical pharmacology pharmacokinetic). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol tartrate. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine.

Hydralazine

Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol tartrate 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 beta1-selective drugs than with non-selective betablockers.

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 tartrate, 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 tartrate. 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, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers. Betaadrenergic 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 Apo-Metoprolol concurrently, and clonidine treatment is to be discontinued, Apo-Metoprolol should be stopped several days before clonidine is withdrawn.

Antidiabetic drugs and insulin

Beta-blockers may interfere with the usual hemodynamic response to hypoglycemia and produce a rise in blood pressure associated with severe bradycardia. In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a beta1-selective drug such as Apo-Metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving Apo-Metoprolol should be monitored to ensure that diabetes control is maintained (see also section 4.4 Special Warnings and Precautions for use).

Lidocaine (xylocaine)

Metoprolol tartrate 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 Apo-Metoprolol.

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

Apo-Metoprolol may modify the pharmacokinetic parameters of alcohol.

4.6 Fertility, pregnancy and lactation

Fertility

Women of child-bearing potential

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

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

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

Lactation

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

4.7 Effects on ability to drive and use machinery

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

4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials

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

Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia
Psychiatric disorders	
Rare	Depression, Nightmares
Very rare	Personality disorder, hallucinations
Nervous system disorders	
Common	Dizziness, headache
Rare	Depressed level of consciousness, somnolence or insomnia, paraesthesia
Eye disorders	
Very rare	Visual impairment (e.g. blurred vision) dry eyes, eye irritation

Ear and labyrinth disorders	
Very rare	Tinnitus ¹ hearing disorders (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	Bradycardia
Rare	Cardiac failure, arrhythmia, palpitation
Very rare	Conduction disorders chest pain
Vascular Disorders	
Common	Orthostatic hypotension (occasionally with syncope)
Rare	Oedema. Raynaud's phenomenon
Very rare	Gangrene ²
Respiratory thoracic and mediastinal disorders	
Common	Exertional dyspnoea
Rare	Bronchospasm ³
Very rare	Rhinitis
Gastrointestinal Disorders	
Common	Nausea and vomiting, abdominal pain
Rare	Diarrhea or constipation
Very rare	Dry mouth, retroperitoneal fibrosis ⁴
Hepatobiliary disorders	
Very rare	Hepatiis
Skin and subcutaneous tissue disorders	
Rare	Rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	Photosensitivity reaction, hyperhydrosis alopecia, worsening of psoriasis
Musculoskeletal and connective tissue disorders	
Rare	Muscle spasms
Very rare	Arthritis
Reproductive system and breast disorders	
Very rare	Erectile dysfunction, libido disorder, Peyronie's disease ⁴
General disorders and administration site conditions	
Common	Fatigue
Investigations	
Very rare	Weight increase, liver function test abnormalities

1 and, in doses exceeding those recommended

2 in patients with pre-existing severe peripheral circulatory disorders

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

4 relationships to Metoprolol tartrate has not been definitely established

Adverse drug reactions from spontaneous reports and literature cases (frequency not known): The following adverse reactions have been derived from post-marketing experience with 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.

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

Nervous system disorders

Confusional state

Investigations

Blood triglycerides increased, High Density Lipoprotein (HDL) decreased

Reporting of suspected adverse reactions:

Reporting 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

Signs and symptoms

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

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

The first manifestations of overdose appear 20 minutes to 2 hours after ingestion of Apo-Metoprolol.

The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Management

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

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

Atropine may be given intravenously to control significant bradycardia. Intravenous betaagonists 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 Special Warnings and Precautions for use) may occur after overdose.

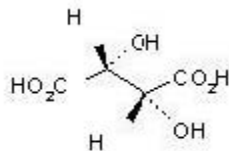
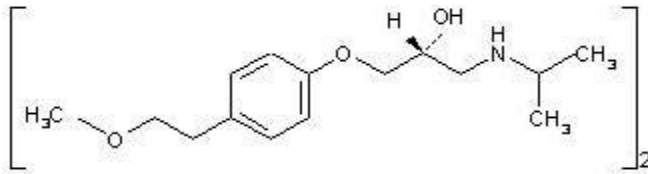
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Cardioselective beta-blocker

Chemical Structure:



Chemical name: di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol] L(+)-tartrate

Molecular Formula (C₁₅H₂₅NO₃)₂·(C₄H₆O₆)

CAS Registry Number: .56392-17-7

Molecular weight: 684.81

Actions

Mechanism of action (MoA)

Metoprolol is a cardioselective beta-blocker; it blocks beta₁-adrenergic receptors (which are mainly located in the heart) at lower doses than those needed to block beta₂-receptors, which are mainly located in the bronchi and peripheral vessels. It has no membrane-stabilising effect nor partial agonist (intrinsic sympathomimetic) activity.

Pharmacodynamics (PD)

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

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

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

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

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

Long-term treatment with metoprolol may reduce insulin sensitivity. However, metoprolol interferes with insulin release and carbohydrate metabolism less than non-selective betablockers. In short-term studies it has been shown that metoprolol may alter the blood lipid profile. It may cause an increase in triglycerides and a decrease in free fatty acids; in some cases, a small decrease in the high-density lipoprotein (HDL) fraction has been observed, although to a lesser extent than with non-selective beta-blockers. In one long-term study lasting several years, cholesterol levels were found to be reduced. Pharmacokinetic and pharmacodynamic studies indicate that 30% of maximum beta-1- adrenoreceptor antagonistic activity is essential for minimum pharmacodynamic effect which is observed with about 45 nmol/L metoprolol in plasma.

5.2 Pharmacokinetics Properties

Absorption

Following oral administration of conventional tablet, metoprolol is rapidly and almost completely absorbed from the gastrointestinal tract. The drug is absorbed evenly throughout gastrointestinal tract. Absorption of metoprolol from with sustained-release metoprolol tartrate tablets, absorption is slower, but the availability of metoprolol is similar compared with conventional tablets. Peak plasma concentrations are attained after approximately 1.5 to 2 hours with conventional metoprolol tablets, and after approximately 4 to 5 hours with sustained-release tablets.

Plasma concentrations of metoprolol increase approximately in proportion with the dose in the 50-mg to 200-mg dose range. Owing to extensive hepatic first-pass metabolism, approximately 50% of a single oral dose of metoprolol reaches the systemic circulation. The extent of presystemic elimination differs between individuals because of genetic differences in oxidative metabolism. Although the plasma profiles exhibit wide intersubject variability, they are reproducible within an individual. Following repeated administration, the percentage of the dose systemically available is approximately 40% higher than after a single dose (that is, approximately 70%). This may be due to partial saturation of the first-pass metabolism, or reduced clearance as a result of reduced hepatic blood flow. Ingestion with food may increase the systemic availability of a single oral dose by approximately 20% to 40%.

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

Distribution

Metoprolol is extensively and rapidly distributed, with a reported volume of distribution of 3.2 to 5.6 L/kg. The apparent volume of distribution at steady-state (V_{ss}) in extensive metabolizers (4.84 L/kg) is relatively higher than poor metabolizers (2.83 L/kg). The half-life is not dose-dependent and does not change on repeated dosing. Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk (see section 4.6 Fertility, pregnancy and lactation). In patients with hypertension, metoprolol concentrations in cerebrospinal fluid are similar to those in plasma. Metoprolol is not a significant P-glycoprotein substrate indicating that inter-individual variability in pharmacokinetics of metoprolol can be majorly due to CYP2D6 metabolism.

Biotransformation/ Metabolism

Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The main metabolic pathways of metoprolol are alpha-hydroxylation, O-demethylation, and oxidative deamination. Alpha-hydroxylation of metoprolol is stereo-selective. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6)..

However, the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol contribute significantly to its beta-blocking effect.

Elimination

The average elimination half-life of metoprolol is 3 to 4 hours; in poor metabolisers the half-life may be 7 to 9 hours. Following single oral administration of 100 mg metoprolol the median clearance was 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultrarapid metabolizers, respectively. The renal clearance of the stereo-isomers does not exhibit stereo-selectivity in renal excretion.

Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolisers), less than 5% of an oral dose, and less than 10% of an intravenous dose, is excreted as unchanged drug. In poor metabolisers, up to 30% or 40% of oral or intravenous doses, respectively, may be excreted unchanged. The total plasma clearance of metoprolol after intravenous administration is approximately 1 L/min.

Dose proportionality

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

Food effect

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

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

Special population

Geriatric patients

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

Patients with renal impairment

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

Patients with hepatic impairment

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

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

Patients with inflammatory disease

Inflammatory disease has no effect on the pharmacokinetics of metoprolol.

Patients with hyperthyroidism

Hyperthyroidism may increase the presystemic clearance of metoprolol.

Ethnic sensitivity

The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizer phenotype.

Approximately 7% of Caucasians and less than 1% Orientals are poor metabolizers. CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizer with normal CYP2D6 activity.

5.3 Preclinical safety data

Reproductive toxicity

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

Mutagenicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Silica-colloidal anhydrous
Microcrystalline cellulose
Croscarmellose sodium
Pregelatinised maize starch
Sodium starch glycollate
Magnesium stearate
Hypromellose
Purified talc
Macrogol 400
Titanium dioxide

Apo-Metoprolol 50 mg tablets also contain iron oxide red C177491.

6.2 Incompatibilities

NIL

6.3 Shelf-Life

3 years from the date of manufacture.

6.4 Special precautions for storage

Store at or below 30°C
Protect from moisture and light

6.5 Nature and contents of container

Apo-Metoprolol 50mg tablets: Blister packs of 100 tablets.
Apo-Metoprolol 100mg tablets: Blister packs of 60 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd
32 Hillside Road
Wairau Valley
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

9. DATE OF FIRST APPROVAL

03 September 2015

10. DATE OF REVISION OF THE TEXT

10 October 2018

Summary Table of Changes

Section changed	Summary of new information
3	Removed 'B' and 'L' separated by Change embossed to debossed
Whole data sheet	Change to new format