PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-METOPROLOL

Metoprolol Tartrate Tablets

Tablets, 25 mg, 50 mg and 100 mg, Oral

USP

[Pr]APO-METOPROLOL (Type L)

Metoprolol Tartrate Film-Coated Tablets

Film-Coated Tablets, 50 mg and 100 mg, Oral

USP

Beta-Adrenergic Receptor Blocking Agent

APOTEX INC.
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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Hypertension

APO-METOPROLOL / APO-METOPROLOL (Type L) (metoprolol tartrate) is indicated for mild or moderate hypertension. Usually combined with other antihypertensive agents (thiazide diuretics), it may be tried alone when the physician judges that a beta-blocker, rather than a diuretic, should be the initial treatment.

Combining metoprolol tartrate with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than metoprolol tartrate alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with metoprolol tartrate.

APO-METOPROLOL / APO-METOPROLOL (Type L) is not recommended for the emergency treatment of hypertensive crises.

Angina Pectoris

APO-METOPROLOL / APO-METOPROLOL (Type L) is indicated for the long-term treatment of angina pectoris due to ischemic heart disease.

Myocardial Infarction

APO-METOPROLOL / APO-METOPROLOL (Type L) is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction, to reduce cardiovascular mortality.

In patients with proven myocardial infarction, oral treatment can begin within 3 to 10 days of the acute event (see 4 DOSAGE AND ADMINISTRATION). Data are not available as to whether benefit would ensue if the treatment is initiated later.

Clinical trials have shown that patients with unconfirmed myocardial infarction received no benefit from early metoprolol tartrate therapy.

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution is indicated when using APO-METOPROLOL / APO-METOPROLOL (Type L) in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

2 CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container or other beta-blockers (cross-sensitivity between beta-blockers can occur). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

APO-METOPROLOL / APO-METOPROLOL (Type L) (metoprolol tartrate) is contraindicated in patients with:

- Sinus bradycardia
- Sick sinus syndrome
- Second and third degree A-V block
- Right ventricular failure secondary to pulmonary hypertension
- Overt heart failure
- Cardiogenic shock
- Severe peripheral arterial circulatory disorders
- Anesthesia with agents that produce myocardial depression, (e.g., ether)
- Pheochromocytoma in the absence of alpha-blockade

Myocardial Infarction Patients - Additional Contraindications

APO-METOPROLOL / APO-METOPROLOL (Type L) is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (PR interval ≥ 0.24 s); systolic blood pressure < 100 mmHg; or moderate to severe cardiac failure (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- For the 50 mg and 100 mg immediate release strengths and the 5 mL ampoules (1 mg/mL), only generic metoprolol tartrate are available in the marketplace.

4.2 Recommended Dose and Dosage Adjustment

Hypertension

APO-METOPROLOL / APO-METOPROLOL (Type L) (metoprolol tartrate) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone (see 1 INDICATIONS).

The dose must always be adjusted to the individual requirements of the patient, in accordance with the following guidelines.

APO-METOPROLOL / APO-METOPROLOL (Type L) treatment should be initiated with doses of 50 mg b.i.d. If an adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded. The usual maintenance dose is within the range of 100 to 200 mg daily.

When metoprolol tartrate is combined with another antihypertensive agent which is already being administered, metoprolol tartrate should be added initially at a dose of 50 mg b.i.d. After one or two weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than two weeks, until adequate blood pressure control is obtained.

Given the interactions of metoprolol tartrate with food, it is recommended that the drug should be administered with or immediately following meals (see 9 DRUG INTERACTIONS, 10 CLINICAL PHARMACOLOGY).

APO-METOPROLOL / APO-METOPROLOL (Type L) tablets should be taken once daily in the morning.

Angina Pectoris

The recommended dosage range for APO-METOPROLOL / APO-METOPROLOL (Type L) in angina pectoris is 100 to 400 mg per day in divided doses. Treatment should be initiated with 50 mg b.i.d. for the first week. If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The usual maintenance dose is 200 mg/day. The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in two or three divided doses. An APO-METOPROLOL / APO-METOPROLOL (Type L) dose of 400 mg/day should not be exceeded.

APO-METOPROLOL / APO-METOPROLOL (Type L) tablets should be taken once daily in the morning.

Myocardial Infarction

In addition to the usual contraindications:

ONLY PATIENTS WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION WHO MEET THE FOLLOWING CRITERIA ARE SUITABLE FOR THERAPY AS DESCRIBED BELOW:	
Systolic Blood Pressure	≥ 100 mmHg
Heart Rate *	≥ 45 beats per minute
PR Interval	< 0.24 seconds
Rales*	< 10 cm
Adequate peripheral circulation	

*Extreme caution should be exercised when giving intravenous metoprolol to patients with heart rate between 45 and 60 and/or pulmonary rales less than 10 cm.

Therapy should be discontinued in patients if the heart rate drops below 45 or the systolic blood pressure drops below 100 mmHg.

Early Treatment

APO-METOPROLOL / APO-METOPROLOL (Type L) is not intended for early treatment.

During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each. The injections should be given at approximately 2-minute intervals. During the intravenous administration of metoprolol tartrate, blood pressure, heart rate, and electrocardiogram should be carefully monitored. If any of the injections are associated with adverse cardiovascular effects, intravenous administration should be stopped immediately and the patient should be observed carefully and appropriate therapy instituted.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily *(see **Late Treatment** below)*.

Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe

intolerance, treatment with metoprolol tartrate should be discontinued (see 7 WARNINGS AND PRECAUTIONS).

Late Treatment (For proven myocardial infarction patients only)

Patients with contraindications to treatment during the early phase of myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Treatment can begin within 3 to 10 days of the acute event. Therapy should be continued for at least 3 months. Although the efficacy of treatment with metoprolol tartrate beyond 6 months has not been conclusively established data from studies with other beta-blockers suggest that the treatment should be continued for 1 to 3 years.

Special populations

Pediatric patients

No pediatric studies have been performed. The safety and efficacy of metoprolol tartrate in pediatric patients have not been established.

Renal impairment

No dose adjustment of APO-METOPROLOL / APO-METOPROLOL (Type L) is required in patients mild to moderate renal impairment. Caution and regular monitoring of renal function are required in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY).

Hepatic impairment

Metoprolol tartrate blood levels are likely to increase substantially in patients with mild to moderate hepatic impairment. Therefore, APO-METOPROLOL / APO-METOPROLOL (Type L) should be initiated at low doses with cautious gradual dose titration according to clinical response and safety monitoring. Patients with severe hepatic impairment should be treated with caution i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs (see 10 CLINICAL PHARMACOLOGY).

Geriatric patients (>65 years)

APO-METOPROLOL / APO-METOPROLOL (Type L) should be given with caution in geriatric patients due to increased likelihood of adverse events. Lower starting and maintenance doses and safety monitoring are recommended (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

For oral use.

APO-METOPROLOL / APO-METOPROLOL (Type L) tablets should be swallowed whole without being chewed, preferably with or following a meal. APO-METOPROLOL / APO-METOPROLOL (Type L) tablets should be taken in the morning.

4.5 Missed Dose

The missed dose of APO-METOPROLOL / APO-METOPROLOL (Type L) should be taken as soon as the patient remembers. However, a missed dose should be omitted if the next dose is due at the same time. Patients should not take a double dose.

5 OVERDOSAGE

Symptoms

The most common signs to be expected with overdosage of a beta-adrenoreceptor agent are hypotension, bradycardia, congestive heart failure, myocardial infarction, bronchospasm and hypoglycemia. Atrioventricular block, cardiogenic shock and cardiac arrest may develop. In addition, impairment of consciousness (or even coma), convulsions, nausea, vomiting and cyanosis and death may occur.

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

The first manifestations of overdosage set in 20 minutes to 2 hours after drug administration.

Management

If overdosage occurs, in all cases therapy with APO-METOPROLOL / APO-METOPROLOL (Type L) should be discontinued, the patient hospitalized and observed closely. Remove any drug remaining in the stomach by induction of emesis or gastric lavage.

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

For management of a suspected drug overdose, contact your regional poison control centre.

Bradycardia and Hypotension: Initially 1 to 2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, norepinephrine or dopamine may be administered after preceding treatment with atropine (see 7 WARNINGS AND PRECAUTIONS

concerning the use of epinephrine in beta-blocked patients). In case of hypoglycemia glucagon (1 to 10 mg) can be administered.

Heart Block (second- or third- degree): Isoproterenol or transvenous cardiac pacemaker.

1. Congestive Heart Failure: Conventional therapy.
2. Bronchospasm: Intravenous aminophylline or a beta$_2$-agonist.
3. Hypoglycemia: Intravenous glucose.

It should be remembered that metoprolol tartrate is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of APO-METOPROLOL / APO-METOPROLOL (Type L). However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Immediate- release tablets, 25 mg, 50 and 100 mg	Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.
	Film-coated tablets, 50 mg, 100 mg	Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. In addition to the above, the Type L 50 mg tablet contains carnauba wax, D & C Red # 30 Aluminum Lake 30%, hydroxypropyl methylcellulose, polyethylene glycol, Sunset Yellow Aluminum Lake 40% and titanium dioxide. Type L 100 mg tablet also contains carnauba wax, hydroxypropyl methylcellulose, Indigotine Aluminum Lake 12-14% (Blue #2), polydextrose, polyethylene glycol and titanium dioxide.

APO-METOPROLOL 25 mg: Each white, oval, biconvex tablet, scored and engraved ‘ME ’over ‘25’ on one side and ‘APO’ on the other, contains 25 mg metoprolol tartrate. Available in bottles of 100, 500 and 1000 tablets.

APO-METOPROLOL 50 mg: Each white, round, biconvex, scored tablet engraved 'APO' over 'M50' on one side contains 50 mg metoprolol tartrate. Available in bottles of 100 and 1000 and in unit dose packages of 100 (10x10) tablets.

APO-METOPROLOL 100 mg: Each white, round, biconvex, scored tablet engraved 'APO' over 'M100' on one side contains 100 mg metoprolol tartrate. Available in bottles of 100 and 1000 and in unit dose packages of 100 (10x10) tablets.

APO-METOPROLOL (Type L) 50 mg: Each pink, capsule shaped, biconvex, scored, film coated tablet engraved '50' on one side contains 50 mg metoprolol tartrate. Available in bottles of 100 and 1000 and in unit dose packages of 100 (10x10) tablets.

APO-METOPROLOL (Type L) 100 mg: Each blue, capsule shaped, biconvex, scored, film coated tablet engraved '100' on one side contains 100 mg metoprolol tartrate. Available in bottles of 100 and 1000 and in unit dose packages of 100 (10x10) tablets.

7 WARNINGS AND PRECAUTIONS

Abrupt withdrawal

Patients with angina or hypertension should be warned against abrupt discontinuation of APO-METOPROLOL / APO-METOPROLOL (Type L). There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of APO-METOPROLOL / APO-METOPROLOL (Type L) is planned in patients with angina pectoris or previous myocardial infarction, the dosage should be gradually reduced over a period of about two weeks. The patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, metoprolol tartrate therapy should be discontinued stepwise and with closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with APO-METOPROLOL / APO-METOPROLOL (Type L) be reinstituted promptly, at least temporarily.

Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it is prudent not to discontinue APO-METOPROLOL / APO-METOPROLOL (Type L) therapy abruptly even in patients treated only for hypertension.

Cardiovascular

Cardiovascular system: Special caution should be exercised when administering APO-METOPROLOL / APO-METOPROLOL (Type L) to patients with a history of heart failure.

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. The positive inotropic action of digitalis may be reduced by the negative inotropic effect of metoprolol tartrate when the two drugs are used concomitantly. The effects of beta-blockers and digitalis are additive in depressing A-V conduction. This also applies to combinations with calcium-antagonists of the verapamil type or some antiarrhythmics (see 9 DRUG INTERACTIONS).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure and/or hypotension (systolic blood pressure ≤ 90 mmHg). Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, APO-METOPROLOL / APO-METOPROLOL (Type L) therapy should be reduced or withdrawn.

Severe Sinus Bradycardia: Severe sinus bradycardia may occur after $beta_1$-adrenergic receptor blockade with APO-METOPROLOL / APO-METOPROLOL (Type L) because of unopposed vagal activity. Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated, possibly leading to A-V block. In such cases, dosage should be reduced or gradually withdrawn. Atropine, isoproterenol or dobutamine should be considered in patients with acute myocardial infarction.

Prinzmetal's angina: Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris).

***Peripheral Circulatory Disorders*:** Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect (see 2 CONTRAINDICATIONS).

Myocardial Infarction - Additional Warnings

Acute Intervention: During acute intervention in myocardial infarction, intravenous metoprolol should only be used by experienced staff under circumstances where resuscitation and monitoring equipment is available.

Cardiac Failure: Depression of the myocardium with APO-METOPROLOL / APO-METOPROLOL (Type L) may lead to cardiac failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular above). Special caution should be exercised when administering APO-METOPROLOL / APO-METOPROLOL (Type L) to patients with a history of cardiac failure or those with minimal cardiac reserve. Should failure occur, treatment should be as described in 7 WARNINGS AND PRECAUTIONS.

Severe Sinus Bradycardia: Severe sinus bradycardia may occur with APO-METOPROLOL / APO-METOPROLOL (Type L) use (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular above). Acute myocardial infarction (particularly inferior infarcts) may significantly decrease sinus rate. If the rate falls below 40 beats/min, especially with signs of decreased cardiac output, administer atropine (0.25 to 0.5 mg) intravenously. If atropine treatment is unsuccessful, discontinue APO-METOPROLOL / APO-METOPROLOL (Type L) and consider cautious administration of isoproterenol or installation of a cardiac pacemaker.

A-V Conduction: APO-METOPROLOL / APO-METOPROLOL (Type L) slows A-V conduction and may produce significant first- (PR interval ≥ 0.24 sec), second-, or third-degree heart block. Acute myocardial infarction may also produce heart block. If heart block occurs, discontinue APO-METOPROLOL / APO-METOPROLOL (Type L) and administer atropine (0.25 to 0.5 mg) intravenously. If atropine treatment is unsuccessful, consider cautious administration of isoproterenol or installation of a cardiac pacemaker. Because of their negative effect on atrioventricular conduction, beta-blockers, including APO-METOPROLOL / APO-METOPROLOL (Type L), should only be given with caution to patients with first degree atrioventricular block.

Hypotension*:* If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, APO-METOPROLOL / APO-METOPROLOL (Type L) should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or A-V block, treatment should be directed at reversing these (see above).

Driving and operating machinery

Dizziness, fatigue or visual impairment may occur during treatment with APO-METOPROLOL / APO-METOPROLOL (Type L) (see 8 ADVERSE REACTIONS) and may adversely affect the patient's ability to drive or use machines.

Patients should be advised to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to APO-METOPROLOL / APO-METOPROLOL (Type L) therapy has been determined.

Endocrine and Metabolism

Thyrotoxicosis: Although metoprolol has been used successfully for the symptomatic (adjuvant) therapy of thyrotoxicosis, possible deleterious effects from long-term use of metoprolol tartrate have not been adequately appraised. Beta-blockade may mask the clinical signs of continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of metoprolol tartrate may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

***Diabetic patients*:** APO-METOPROLOL / APO-METOPROLOL (Type L) should be administered cautiously to patients subject to spontaneous hypoglycemia or diabetic patients who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blockers, including APO-METOPROLOL / APO-METOPROLOL (Type L), affect glucose metabolism and may mask the premonitory signs and symptoms of acute hypoglycemia, such as tachycardia. 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 adjustment. Diabetic patients receiving APO-METOPROLOL / APO-METOPROLOL (Type L) should be monitored to ensure that diabetes control is maintained.

Pheochromocytoma: Where a beta-blocker is prescribed for a patient known to be suffering from a pheochromocytoma, an alpha-blocker should be given concomitantly. A beta-blocker should be initiated only after the alpha-blocker has been initiated.

Hepatic/Biliary/Pancreatic

Metoprolol tartrate is mainly eliminated by means of hepatic metabolism (see 10.3 Pharmacokinetics).

***Hepatic impairment*:** may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Therefore, APO-METOPROLOL / APO-METOPROLOL (Type L) should be used with caution in patients with impaired liver function. Liver function tests should be performed at regular intervals during long-term treatment (see 10.3 Pharmacokinetics). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Therefore, dose adjustment and regular monitoring of hepatic function are advised in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should be treated with caution i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs.

Immune

***Anaphylactic reactions*:** There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. Whenever possible, beta-blockers, including APO-METOPROLOL / APO-METOPROLOL (Type L), should be avoided in patients who are at risk of anaphylaxis. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm.

Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta-agonists including parenteral salbutamol or isoproterenol, to overcome bronchospasm and norepinephrine to overcome hypotension.

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 9 DRUG INTERACTIONS). Patients taking an oral calcium channel blocker of the verapamil type in combination with APO-METOPROLOL / APO-METOPROLOL (Type L) should be closely monitored. See the complete list of observed and potential drug-drug and other drug interactions with metoprolol tartrate in 9 DRUG INTERACTIONS section.

Peripheral vascular disease:

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see 2 CONTRAINDICATIONS).

Peri-Operative Considerations

***Anesthesia and Surgery*:** The necessity or desirability of withdrawing beta-blocking agents prior to major surgery is controversial. The impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anaesthesia and surgical procedures. The benefits of continuing a treatment with a beta-blocker should be balanced against the risk of withdrawing it in each patient. However, care should be taken to avoid using anesthetic agents that may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.).

In patients receiving beta-blocker therapy, inhalation anaesthetics may enhance the cardiodepressant effect. Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance 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.

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 therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Since metoprolol is a competitive inhibitor of beta-adrenoceptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or dobutamine.

Renal

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 and safety monitoring in patients with severe renal impairment, including renal failure.

Respiratory

Bronchospastic Diseases: **In general, patients with bronchospastic diseases should not receive beta-blockers, including APO-METOPROLOL / APO-METOPROLOL (Type L)**. However, because of its relative $beta_1$-selectivity, APO-METOPROLOL / APO-METOPROLOL (Type L) may be used with caution in patients with asymptomatic bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should preferably be administered concomitantly, and the lowest possible dose of APO-METOPROLOL / APO-METOPROLOL (Type L) should be used. In these circumstances it would be prudent initially to administer APO-METOPROLOL / APO-METOPROLOL (Type L) in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see 4 DOSAGE AND ADMINISTRATION).

Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically in patients with proven or suspected acute myocardial infarction. If bronchospasm not related to congestive heart failure occurs, APO-METOPROLOL / APO-METOPROLOL (Type L) should be discontinued. A theophylline derivative or a $beta_2$-agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$-agonists may produce serious cardiac arrhythmias.

Skin

Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported with beta-blockers, including metoprolol tartrate. Oculomucocutaneous syndrome, a severe syndrome whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic receptor-blocking agent (practolol). This syndrome has not been observed with metoprolol tartrate or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur (see 7 WARNINGS AND PRECAUTIONS-*Abrupt withdrawal*).

7.1 Special Populations

7.1.1 Pregnant Women

Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor and stop gradually taking the drug. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against the possible hazards.

There is a limited amount of data on the use of metoprolol in pregnant women. Metoprolol crosses the placental barrier. Since metoprolol tartrate has not been studied in human pregnancy, the drug should not be given to pregnant women.

7.1.2 Breast-feeding

Metoprolol is excreted in breast milk. If drug use is essential, patients should stop nursing.

7.1.3 Pediatrics

Pediatrics (0 to 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution is indicated when using APO-METOPROLOL / APO-METOPROLOL (Type L) in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels. Lower starting and maintenance doses and safety monitoring are advised in these patients (see 1 INDICATIONS, 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse events reported are exertional tiredness, gastrointestinal disorders, and disturbances of sleep patterns. The most serious adverse events reported are congestive heart failure, bronchospasm and hypotension.

Reported adverse events according to organ systems are:

Table 3 - Reported adverse events according to organ systems

Cardiac disorders	Secondary effects of decreased cardiac output which include: syncope, vertigo, light-headedness and postural hypotension; Significant Conduction disorders (First, Second and Third degree A-V block) (2 CONTRAINDICATIONS); Congestive heart failure (7 WARNINGS AND PRECAUTIONS); Severe bradycardia; Hot flushes; Arrhythmias; Lengthening of PR interval; Palpitations; Sinus arrest; Cold extremities; Claudication; Chest pain
Vascular disorders	Raynaud's phenomenon; Gangrene in patients with pre-existing severe peripheral circulatory disorders; Oedema
Psychiatric disorders	Mental depression; Vivid dreams / nightmares; Hallucination; Personality disorder
Nervous System disorders	Headache, Weakness, Dizziness, Sedation, Light-headedness, Somnolence, insomnia, Vertigo, Paresthesia, Anxiety, Depressed level of consciousness
Gastrointestinal disorders	Diarrhea, Abdominal pain, Constipation, Heartburn, Flatulence, Dry mouth, Nausea and vomiting, Retroperitoneal fibrosis
Hepatobiliary disorders	Hepatitis
Respiratory disorders	Shortness of breath; Wheezing; Bronchospasm; Rhinitis; Status asthmaticus; Exertional dyspnea
Skin and subcutaneous tissue disorders (7 WARNINGS AND PRECAUTIONS)	Rash (exanthema, urticaria, psoriasiform and dystrophic skin lesions); Hyperhydrosis; Pruritus; Photosensitivity reaction; Alopecia; Worsening of psoriasis
Musculoskeletal and connective tissue disorders	Muscle spasms; Arthritis

Reproductive system and breast disorders	Erectile dysfunction; Libido disorder; Peyronie's disease
Ear and labyrinth disorders	Tinnitus; Hearing disorders (e.g. hypoacusis or deafness) when doses exceed those recommended
Eye disorders	Dry eyes, eye irritation; Visual impairment (e.g. blurred vision); Conjunctivitis
General disorders and administration site conditions	Fatigue; Exertional tiredness
Metabolism	Weight increase

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In a placebo-controlled study in patients with acute myocardial infarction the incidence of the following cardiovascular reactions were:

Table 4 – The incidence of cardiovascular reactions in a placebo-controlled study with patients with acute myocardial infarction

	Metoprolol	Placebo
Cardiovascular		
Orthostatic hypotension (systolic BP <90 mmHg)	27.4%	23.2%
Bradycardia (heart rate <40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (PR ≥ 0.24 s)	5.3%	1.9%
Cardiac failure	27.5%	29.6%

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Laboratory

The following laboratory parameters have been elevated on rare occasions: transaminases, BUN, alkaline phosphatase and bilirubin.

Hematology

Isolated cases of thrombocytopenia and leucopenia.

8.5 Post-Market Adverse Reactions

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 voluntary 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant administration of APO-METOPROLOL / APO-METOPROLOL (Type L) and intravenous calcium channel blockers (e.g., verapamil, diltiazem) may increase the risk of cardiac arrest (see 9.4 Drug-Drug Interactions).
- Inhalation anesthetics may enhance cardio-depressant effect of APO-METOPROLOL / APO-METOPROLOL (Type L) (see 9.4 Drug-Drug Interactions).
- Concomitant use of APO-METOPROLOL / APO-METOPROLOL (Type L) and digitalis glycosides may result in excessive bradycardia and/or an increase in AV conduction time (see 9.4 Drug-Drug Interactions).

9.2 Drug-Interactions Overview

Metoprolol is a substrate of CYP2D6 enzyme, therefore potent inhibitors of this enzyme may increase metoprolol concentration. Concomitant use of glycosides, clonidine, calcium channel blockers and fingolimod with beta-blockers can increase the risk of bradycardia. Beta-blockers including metoprolol, may exacerbate the rebound hypertension that can follow the withdrawal

of clonidine. MAO inhibitors or catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents. Beta-blockers may potentiate the negative inotropic effect of anti-arrhythmic agents and their effect on atrial-conduction time.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 5 - Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical comment
Alcohol	C	Increased concentration of metoprolol in blood	Metoprolol modifies the pharmacokinetics (decreases the elimination rate) of alcohol. Which *may* increase certain side effects of metoprolol
Aldesleukin or other drugs known to decrease blood pressure	T	↑ hypotensive effect of metoprolol tartrate	Concomitant administration of beta-blockers with other drugs known to decrease blood pressure such as aldesleukin may result in an enhanced hypotensive effect.
Anti-adrenergic agents	C	Potentiate antihypertensive effect of alpha-adrenergic blockers	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. Withdrawing the beta-blocker several days before the clonidine may reduce the danger of rebound effects.
Antiarrhythmic Agents	C	Potentiate the negative inotropic effect of anti-	Beta-blockers may potentiate the negative inotropic effect of anti-

Proper Name	Ref	Effect	Clinical comment
		arrhythmic agents and their effect on atrial-conduction time	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 antiarrhythmic agents such as quinidine, tocainide, procainamide, ajmaline amiodarone, flecainide and disopyramide may potentiate the effects of metoprolol tartrate on heart rate and atrioventricular conduction.
Other Antihypertensive drugs	CT	Hypotension	APO-METOPROLOL / APO-METOPROLOL (Type L) dosage should be adjusted to the individual requirements of the patient especially when used concomitantly with other antihypertensive agents (4 DOSAGE AND ADMINISTRATION). Patients receiving concurrent treatment with catecholamine depleting drugs, other beta-blockers (including those in form of eye drops, such as timolol), should be carefully monitored.
Calcium Channel Blockers (IV Use)	CT	Potentiate the depressant effects of beta-blockers	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 / APO-METOPROLOL (Type L) because there is a risk of cardiac arrest in this situation. However, in exceptional cases,

Proper Name	Ref	Effect	Clinical comment
			when the physician considers concomitant use essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists. Verapamil and diltiazem reduce metoprolol clearance (7 WARNINGS AND PRECAUTIONS).
Calcium channel blockers (oral use)	CT	Additive reduction in myocardial contractility	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 / APO-METOPROLOL (Type L) should be closely monitored.
CYP2D6 inhibitors	CT	↑ plasma concentration of metoprolol	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 (see 10 CLINICAL PHARMACOLOGY). 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,

Proper Name	Ref	Effect	Clinical comment
			antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinine, antifungals such as terbinafine.
Digitalis glycosides	C	Excessive bradycardia and/or ↑ in atrioventricular conduction time	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.
Dipyridamole	C	Careful monitoring of heart rate	In general, administration of a beta-blocker should be withheld before dipyridamole testing, with careful monitoring of heart rate following the dipyridamole injection.
Ergot alkaloid	C	↑vasoconstrictive action of ergot alkaloids	Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.
Fingolimod	CT/C	bradycardia	Concomitant administration of beta-blockers with other drugs known to decrease heart rate such as sphingosine-1-phosphate receptor modulators (e.g. fingolimod) may result in additive heart rate lowering effects and is not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.
Hepatic Enzyme-Inducers	CT	Influence plasma level of metoprolol	Hepatic enzyme-inducing substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by

Proper Name	Ref	Effect	Clinical comment
			rifampicin.
Hydralazine	C	↑ concentrations of metoprolol	Concomitant administration of hydralazine may inhibit presystemic metabolism of metoprolol leading to increased concentrations of metoprolol.
Inhalation anesthetics	C	↑cardiodepression of certain anesthetics	Beta-blockers enhance the cardiodepression produced by certain anesthetics (see 7 WARNINGS AND PRECAUTIONS, Patients Undergoing Surgery).
Lidocaine	C	↓ clearance of lidocaine	Metoprolol may reduce the clearance of lidocaine.
MAO Inhibitors and Adrenergic Neuron Blockers	C	↓ sympathetic activity	Closely monitor patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine). The added beta-adrenergic-blockade of metoprolol may excessively reduce sympathetic activity. APO-METOPROLOL / APO-METOPROLOL (Type L) should not be combined with other beta-blockers.
Nitroglycerin	C	↑ hypotensive effect of metoprolol tartrate	Nitroglycerin may enhance the hypotensive effect of metoprolol tartrate.
NSAIDs	C	↓ antihypertensive effect of beta-blockers	Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker may decrease the antihypertensive effect of beta-blockers, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by non-steroidal anti-inflammatory drugs.
Oral Antidiabetics drugs and insulin	C	↑ blood pressure associated with severe bradycardia	Beta-blockers may interfere with the usual hemodynamic response to hypoglycemia and produce a rise in blood pressure associated with severe bradycardia. The dosage of

Proper Name	Ref	Effect	Clinical comment
			oral antidiabetics may have to be readjusted in patients receiving beta-blockers (see 7 WARNINGS AND PRECAUTIONS).
Prazosin (selective alpha-1-adrenergic antagonist)	C	↑ acute postural hypotension	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 / APO-METOPROLOL (Type L).
Sympathomimetics	C	hypertension	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.

Legend: C = Case Study (Postmarket); CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food enhances the bioavailability of an oral dose of metoprolol by approximately 20 to 40%. Indeed, food intake affects the pharmacokinetics of metoprolol leading to increased exposure (AUC) and a higher maximum plasma concentration (C_{max}) (see 10 CLINICAL PHARMACOLOGY). Hence, in order to minimize the effect variations within the individual, it is recommended that the drug should be administered with or immediately following meals.

In one clinical study with metoprolol immediate release formulation, it was found that C_{max} and AUC were higher by about 32% and 38%, respectively, when administered after standard breakfast as compared to fasting condition. The study recommended that the drug should be administered with or immediately following meals to minimize the variations within an individual.

9.6 Drug-Herb Interactions

The interaction of metoprolol with herbal medications or supplements has not been studied.

9.7 Drug-Laboratory Test Interactions

No data suggest that metoprolol interferes with laboratory tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Metoprolol is a beta-adrenergic receptor-blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on the beta-adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits beta-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol tartrate has no membrane-stabilizing or partial agonism (intrinsic sympathomimetic) activities. It is used in the treatment of hypertension, angina pectoris and to reduce mortality in patients with myocardial infarction.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the beta-receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output;

b) inhibition of renin release by the kidneys;

c) inhibition of the vasomotor centres.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic receptor blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure (preload).

The mechanisms involved in reducing mortality in patients with acute myocardial infarction are not fully understood.

10.2 Pharmacodynamics

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within one hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum effect after single oral doses of 20, 50 and 100 mg occurred at 3.3, 5.0 and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

In 5 healthy volunteers, intravenously-administered 10 mg doses of metoprolol reduced exercise-induced tachycardia by 13% and systolic blood pressure during exercise by 13%. The decrease in mean blood pressure after epinephrine was abolished by metoprolol, whereas the increase in systolic blood pressure was reduced by 50%; vascular resistance in the forearm was unchanged after metoprolol.

In healthy volunteers, intravenous metoprolol 0.15 mg/kg significantly lowered cardiac output by 1.3 litre/min. at rest, and 3.6 litre/min. during exercise. The mean decreases in heart rate were 9 and 16 beats/min. during rest and exercise, respectively. Right atrial pressure was significantly increased during rest and exercise. Oxygen consumption was not significantly influenced by drug administration. Significant increases in the calculated arteriovenous oxygen differences were observed (6 and 20 mL/litre at rest and during exercise, respectively).

A single oral dose of 40 mg of metoprolol administered to 17 anginal patients 90 minutes before testing, increased total work performed from 5994 to 8462 k.p.m. (40%). Times to onset of pain and appearance of ST depression were similarly increased from 11.8 to 16.9 minutes and 9.9 to 13.9 minutes respectively.

Effects on Pulmonary Function

The effects on specific airways resistance (SR_{aw}) of single oral doses of 100 mg of metoprolol were assessed in 6 healthy volunteers and in 12 patients with bronchial asthma. No bronchodilator was used. Metoprolol did not have a significant effect on SR_{aw} in the normal subjects, but in the asthmatic patients, SR_{aw} was significantly increased. Similar findings were observed with an 80 mg dose of propranolol.

In a controlled study, 17 patients with bronchial asthma received concomitantly a bronchodilator (terbutaline) with 50 or 100 mg b.i.d. of metoprolol. The FEV_1 values fell only in the high dose group, indicating some b_2-blocking effect.

Pharmacokinetic and pharmacodynamic relationship

Following intravenous administration of metoprolol tartrate, the half-life of the distribution phase is approximately 12 minutes; the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta-blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol tartrate caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end-diastolic pressure remained unchanged.

The SR formulation produced lower peak metoprolol plasma concentrations than the regular tablets in studies with volunteers. Between 4 to 6 hours, both concentration curves were similar. During the 8 to 24 hour period concentrations were higher with the SR tablets.

10.3 Pharmacokinetics

The drug is available in racemic form and it exhibits stereo-specific pharmacokinetics.

Absorption:

In humans, 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. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Inter-subject plasma levels achieved are highly variable after oral administration, although they show good reproducibility within each individual. Peak plasma concentrations are attained after approximately 1.5 to 2 hours with conventional metoprolol formulations, and after approximately 4 to 5 hours with slow-release formulations. Following repeated oral administration, the percentage of the dose systemically available is higher than after a single dose and also increases dose dependently. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Distribution:

Metoprolol is rapidly and extensively distributed to the extra-vascular tissue. The mean volume of distribution is 3.2 to 5.6 L/kg. The apparent volume of distribution at steady-state (Vss) in extensive metabolizers (4.84 L/kg) is almost 2-fold higher that of poor metabolizers (2.83 L/kg). At therapeutic concentrations, approximately 12 % of the active ingredient in metoprolol tartrate tablets is bound to human serum proteins. Metoprolol crosses the placenta and is found in breast milk (see 7.1.2 Breast-feeding).

Metabolism:

Biotransformation / Metabolism: Metoprolol is not a significant P-glycoprotein substrate but is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6), which causes inter-individual variability in pharmacokinetics and pharmacodynamics of metoprolol.

Indeed, the accumulation of metoprolol leads to high levels of the drug in plasma in poor metabolizers (PMs), which are associated with higher intensity of therapeutic effects, an increase in duration of action and an increase in the occurrence and severity of AEs as compared to extensive metabolizers (EMs).

Metabolism & Dose-proportionality: Metoprolol exhibits saturable pre-systemic metabolism leading to non-proportionate increase in exposure with increased dose. However, dose proportionate pharmacokinetics is expected with extended release formulations.

Food enhances the bioavailability of an oral dose of metoprolol by approximately 20 to 40%. Indeed, food intake affects the pharmacokinetics of metoprolol leading to increased exposure (AUC) and a higher maximum plasma concentration (C_{max}) (see 9 DRUG INTERACTIONS).

In one clinical study with metoprolol immediate release formulation, it was found that C_{max} and AUC were higher by about 32% and 38%, respectively, when administered after standard breakfast as compared to fasting condition. The study recommended that the drug should be administered with or immediately following meals to minimize the variations within an individual.

Elimination:

Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 hours (range: 1 [in EMs] to 9 hours [in PMs]). The total clearance rate of an intravenous dose is approximately 1L/min and the protein binding rate is approximately 10%. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following single oral administration of 100 mg metoprolol the median clearance were 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultrarapid metabolizers, respectively.

Special Populations and Conditions

- **Geriatrics:** The elderly population show higher plasma concentrations of metoprolol (up to 28% AUC increase in elderly patients as compared to young healthy volunteers) as a combined result of a decreased elimination of metoprolol and the metabolite α-hydroxy-metoprolol and a decreased hepatic blood flow due to age-related physiological changes. In addition, time to reach peak concentration, T_{max}, was

significantly longer in the elderly population. Hence, it is recommended to initiate therapy with lower doses in this group and safety monitoring may be recommended.

- **Ethnic Origin (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 metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Orientals are PMs. CYP2D6 poor metabolizers exhibit 5-fold higher plasma concentrations of metoprolol than extensive metabolizers with normal CYP2D6 activity.

- **Hepatic impairment:** Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment impacts 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. Hence, dose adjustment and safety monitoring are advised in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should be treated with caution, i.e. lower initial and maintenance doses as well as regular monitoring of hepatic function, as they are more sensitive to therapeutic effects/adverse effects of drugs.

- **Renal impairment:** Pharmacokinetics of metoprolol in patient with renal impairment did not differ to a clinically significant degree from normal subjects. However, there is accumulation of one of its less active metabolite in patients with a creatinine clearance below 5 mL/min. Since the resulting metabolite accumulation has no significant effect on the beta-blocking effects, metoprolol dosing does not need to be altered in patient with mild to moderate renal impairment. Caution is advised in the use of a beta-blocker in patients with severe renal impairment and safety monitoring is advised in these patients.

11 STORAGE, STABILITY AND DISPOSAL

APO-METOPROLOL / APO-METOPROLOL (Type L): Store at room temperature (15°C to 30°C) and protect from light.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

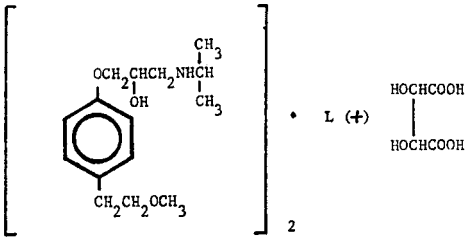
Proper name: Metoprolol tartrate

Chemical name:

1. 2-Propanol, 1-[4-(2-methoxyethyl)phenoxyl]-3-[(1-methylethyl)amino]-, (∀)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate) (2:1) (salt)
2. (±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt);
3. 1-Isopropylamino-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol (2:1) dextro-tartrate salt.

Molecular formula and molecular mass: $C_{34}H_{56}N_2O_{12}$ and 685 g/mol

Structural formula:



Physicochemical properties: Metoprolol is the tartrate salt of an organic base. It is a colourless, odorless, crystalline powder with a bitter taste. At 20°C it is 10% soluble in water. The pH of a 2% aqueous solution is 6.7.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of APO-METOPROLOL 100 mg tablets (Apotex Inc.) and Betaloc® 100 mg tablets (AstraZeneca Canada Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 18 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metoprolol (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	624 817 (82.5)	600 776 (81.3)	100.8	95.2 – 116.5
AUC_I (ng·h/mL)	626 825 (83.9)	602 781 (82.2)	100.8	95.5 – 116.9
C_{max} (ng/mL)	115 129 (51.8)	111 124 (51.8)	100.8	94.0 – 115.0
T_{max}[3] (h)	1.6 (31.6)	1.8 (35.2)		
$T_{½}$[3] (h)	3.4 (33.9)	3.3 (35.4)		

[1] APO-METOPROLOL (metoprolol tartrate) tablets, 100 mg (Apotex Inc.)
[2] Betaloc® (metoprolol tartrate) tablets, 100 mg (AstraZeneca Canada Inc.)
[3] Expressed as the arithmetic mean (CV%) only

A randomized, two-way, single-dose, crossover comparative bioavailability study of APO-METOPROLOL (TYPE L) 100 mg tablets (Apotex Inc.) and Betaloc® 100 mg tablets (AstraZeneca Canada Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 19 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metoprolol (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	839 1113 (78.0)	827 1080 (75.8)	100.2	90.6 – 113.5
AUC_I (ng·h/mL)	853 1158 (83.0)	860 1158 (79.5)	99.9	87.4 – 112.5
C_{max} (ng/mL)	147 168 (53.0)	148 171 (54.7)	99.8	89.9 – 109.3
T_{max}[3] (h)	1.5 (32.4)	1.5 (39.9)		
$T_{½}$[3] (h)	4.0 (56.5)	4.7 (84.6)		

[1] APO-METOPROLOL (TYPE L) (metoprolol tartrate) tablets, 100 mg (Apotex Inc.)
[2] Betaloc® (metoprolol tartrate) tablets, 100 mg (AstraZeneca Canada Inc.)

[3] Expressed as the arithmetic mean (CV%) only

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Table 6 – Acute Toxicity

Species	Sex	Route	Solutions	LD_{50}(mg/kg)
Mouse	Male	I.V.	1%	69.4 ± 5.1
Mouse	Female	I.V.	1%	79.9 ± 4.5
Mouse	Male	P.O.	23%	2460 ± 210
Mouse	Female	P.O.	25%	2300 ± 200
Rat	Male	I.V.	5%	71.9 ± 4.1
Rat	Female	I.V.	5%	74.3 ± 4.4
Rat	Male	P.O.	50%	4670 ± 1210
Rat	Female	P.O.	50%	3470 ± 580

The toxic symptoms in rats include: sedation, ataxia, piloerection, irritation, spasm, and lacrimation. Rats were unconscious before death, which occurred within 5 to 10 minutes after intravenous injection and 6 to 20 hours after oral administration.

In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms, and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection. No symptoms of toxicity were detectable 24 hours after administration in surviving animals.

Table 7 – Long-Term Toxicity (Subacute)

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rats	4	10 M 10 F	Saline, 10, 50, 100/day (after 14 days, high dose increased to 200/day).	P.O.	5 Wks	Slight increase in hematocrit and slight decrease in blood sugar in high-dose females.
Beagle Dogs	1	1 M 1 F	40 x 3 days, increased by 20/day to 140 x 6 days to 160/day.	P.O.	3 Wks	Disturbance of balance; increased abdominal muscular tone, mydriasis, hyperemia in visible mucous membranes. One dog died at dose

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
						level of 140 mg/kg/day.
Beagle Dogs	2	1 M	80 b.i.d. one day; 2 days later, single dose of 100.	P.O.	3 Days	Disturbance of balance; vomiting, prostration, dyspnea, loss of consciousness, death.
		2 F	20 b.i.d. increased every 5 days by 20 b.i.d. up to 120 b.i.d.	P.O.	4 Wks	Vomiting; increased salivation, tremor, ataxia. One dog died at highest dose.
Beagle Dogs	4	1 M 1 F	0, 5, 20, 40/day	P.O.	4 Wks	None.
Beagle Dogs	3	1 M 1 F	Saline, 0.5, 5 /day	I.V.	2 Wks	Prolonged PR interval in ECG.
Beagle Dogs	2	1 M 1 F	Saline, 5 /day	I.V.	2 Wks	Prolonged PR interval in ECG.

Table 8 – Long-Term Toxicity (Subacute)

Strain Species	No. Of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rat	4	15 M 15 F	Saline, 10, 100, 200/day. High dose increased to 200/day after 13 Weeks	P.O.	6 Months	None.
Beagle Dogs	One Control	2 M 2 F	0, 5, 20, 40 b.i.d. After 7 weeks, high dose increased to 50/b.i.d.	P.O.	6 Months	Bradycardia, increased PR interval and QT interval in ECG.
	Three	3 M				

Strain Species	No. Of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
	Active	3 F	After 3 months, intermediate dose increased to 30 b.i.d. and high dose to 80 b.i.d.			
Beagle Dog	One Control	6 M 6 F	0, 10, 60 day. High level dogs received 120 on day 1, 60 on days 3 to 8; 90/day on days 9 to 22 and 105/day for balance.	P.O.	1 Year	2 high-dose dogs died on day 1, otherwise, none.

Carcinogenicity:

Metoprolol was administered to 3 groups of 60 male and 60 female Charles River Sprague-Dawley rats at dietary levels of 50, 200 and 800 mg/kg per day for 78 weeks. A fourth group received 2-AAF (positive control) and the fifth was the negative control group. The incidence of nodules and masses observed at necropsy were comparable between the treated and control groups. The only histopathological changes noted were an increased incidence of impaction of pulmonary alveoli by septal cells in the high and intermediate metoprolol-treated groups. The strain of rats was susceptible to the known carcinogen 2-AAF; a statistically higher incidence of neoplasms, primarily hepatomas, was present.

A similar study in Swiss albino mice at doses of 75, 150 and 750 mg/kg per day for 78 weeks showed that the tumors were distributed with equal frequency in the treated and control groups. The strain was susceptible to the known carcinogen.

Reproductive and Developmental Toxicology:

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 20 pregnant rats on days 6 to 15 of gestation. Treatment with metoprolol did not adversely affect any of the parameters studied.

Rabbit: (New Zealand White strain) Doses of 5, 12.5 and 25 mg/kg were administered orally to groups of 20 pregnant rabbits on days 6 to 18 of gestation. Parameters studied were not significantly affected, although litter size was lower and fetal loss higher in the high dose group. The incidence of fetal abnormality was unaffected by treatment.

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 50 rats from day 15 of gestation, through lactation to 21 days postpartum. Parameters studied in litter and parent animals were not adversely affected.

Rat: (Charles River CD strain) Doses of 50 and 500 mg/kg were administered orally to groups of 10 male and 20 female rats. Males were treated for 63 days prior to mating and during the mating period. The females were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days postpartum, with an interim sacrifice at day 13 of gestation. The only significant finding in this study was a slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day and a higher frequency of stillbirths in the high dose group.

17 SUPPORTING PRODUCT MONOGRAPHS

1. LOPRESOR SR® slow-release tablets, 100 mg and 200 mg, submission control 256174, Product Monograph, Novartis Pharmaceuticals Canada Inc. (FEB 14, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-METOPROLOL

Metoprolol Tartrate Tablets

PrAPO-METOPROLOL (Type L)

Metoprolol Tartrate Film-Coated Tablets

Read this carefully before you start taking **APO-METOPROLOL / APO-METOPROLOL (Type L)** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-METOPROLOL / APO-METOPROLOL (Type L).**

What is APO-METOPROLOL / APO-METOPROLOL (Type L) used for?

APO-METOPROLOL / APO-METOPROLOL (Type L) is used in adults for the following conditions:

- to treat high blood pressure (mild or moderate hypertension). It can be used alone or with other medicines.
- to treat chest pain (angina pectoris) caused by narrowed heart arteries
- to help prevent another heart attack (myocardial infarction)

How does APO-METOPROLOL / APO-METOPROLOL (Type L) work?

APO-METOPROLOL / APO-METOPROLOL (Type L) belongs to a group of medicines known as “beta-blockers”. It works by blocking the effects of certain hormones, such as adrenaline. This causes your heart to beat more slowly and with less force.

What are the ingredients in APO-METOPROLOL / APO-METOPROLOL (Type L)?

Medicinal ingredients: metoprolol tartrate.

Non-medicinal ingredients:

APO-METOPROLOL: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

APO-METOPROLOL (Type L) 50 mg: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D & C Red # 30 Aluminum Lake 30%, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and polyethylene glycol, Sunset Yellow Aluminum Lake 40% and titanium dioxide.

APO-METOPROLOL (Type L) 100 mg: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, Indigotine Aluminum Lake 12-14% (Blue #2), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol and titanium dioxide.

APO-METOPROLOL / APO-METOPROLOL (Type L) comes in the following dosage forms:

Tablets, 25, 50 and 100 mg

Film-Coated Tablets, 50 and 100 mg

Do not use APO-METOPROLOL / APO-METOPROLOL (Type L) if:

- you are allergic to metoprolol tartrate or to any other ingredients in APO-METOPROLOL / APO-METOPROLOL (Type L).
- you are allergic to other beta-blockers.
- you have the following heart or blood vessel problems:
  - bradycardia (abnormally slow heart beat)
  - sick sinus syndrome (heart's natural pacemaker is unable to create normal heartbeats at the normal rate)
  - second or third degree heart block (a type of irregular heart beat and rhythm)
  - right ventricular failure (right side of the heart is not pumping normal amounts of blood to the lungs)
  - heart failure (heart does not pump blood as well as it should)
  - cardiogenic shock (heart is unable to pump enough blood to the organs of the body)
  - severe peripheral arterial disorder (arteries are narrowed which reduces blood flow to your limbs)
- you are receiving anesthesia and are taking medicines that can affect your heart.
- you have a condition known as pheochromocytoma (a tumour in the adrenal gland) and are not being treated with an alpha-blocker.
- you have had a heart attack and also have any of the following:
  - a heart rate of less than 45 beats per minute
  - second or third degree heart block (a type of irregular heart beat and rhythm)
  - systolic blood pressure less than 100 mmHg
  - moderate to severe heart failure

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-METOPROLOL / APO-METOPROLOL (Type L). Talk about any health conditions or problems you may have, including if you:

- have Prinzmetal's angina (a type of chest pain)
- have blood vessel problems (e.g., peripheral arterial disorder)
- have problems with your heart or had a heart attack
- have an overactive thyroid gland (hyperthyroidism)
- have high or low levels of sugar in the blood (diabetes), and are receiving insulin or other medicines to control blood sugar
- have problems with your liver or kidneys are at risk for allergic reactions
- have asthma or a history of breathing problems (such as wheezing and shortness of breath)
- are under 18 years old or are elderly.

Other warnings you should know about:

Stopping your medication: Do not suddenly stop taking APO-METOPROLOL / APO-METOPROLOL (Type L). This could cause chest pains or a heart attack. If your healthcare professional decides that you should stop taking APO-METOPROLOL / APO-METOPROLOL (Type L), your dose will be reduced slowly before you stop taking the medicine completely.

Heart failure (heart does not pump blood as well as it should): Beta-blockers, such as APO-METOPROLOL / APO-METOPROLOL (Type L), can slow your heart rate and cause heart failure, and/or low blood pressure. If you already have heart failure taking this medicine can make it worse. If you notice any signs or symptoms of a heart failure tell your healthcare professional right away. They may prescribe additional medication and will closely monitor your health.

Bradycardia (abnormally slow heart beat): APO-METOPROLOL / APO-METOPROLOL (Type L) can cause severe sinus bradycardia. Tell your healthcare professional if this occurs. They may reduce your dose of APO-METOPROLOL / APO-METOPROLOL (Type L). They will tell you how to safely stop your treatment with APO-METOPROLOL / APO-METOPROLOL (Type L).

Driving and using machines: If you experience dizziness, tiredness or blurred vision during your treatment with APO-METOPROLOL / APO-METOPROLOL (Type L), do not drive, use machinery, or perform other tasks that need full attention until you know how you respond to APO-METOPROLOL / APO-METOPROLOL (Type L).

Anesthesia and surgery: If you are going to have surgery where an anesthetic will be used, tell your healthcare professional that you are taking APO-METOPROLOL / APO-METOPROLOL (Type L).

Severe skin reactions: APO-METOPROLOL / APO-METOPROLOL (Type L) can cause a variety of severe skin reactions such as rashes and severe skin dryness. If you notice any signs and

symptoms of a skin reaction, tell your healthcare professional. They will tell you how to safely stop your treatment with APO-METOPROLOL / APO-METOPROLOL (Type L).

Pregnancy and breastfeeding: You should not take APO-METOPROLOL / APO-METOPROLOL (Type L) during pregnancy or if you are breastfeeding. Tell your healthcare professional if you are:

- pregnant,
- able to become pregnant,
- breastfeeding, or
- planning to breastfeed.

Blood tests and monitoring: Based on your health history, your healthcare professional may perform blood tests for as long as you are being treated with APO-METOPROLOL / APO-METOPROLOL (Type L). They may monitor:

- your blood sugar
- how well your heart, liver, kidney and thyroid are working
- how APO-METOPROLOL / APO-METOPROLOL (Type L) is affecting other medications that you are taking.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking APO-METOPROLOL / APO-METOPROLOL (Type L) with:

- calcium channel blockers (such as verapamil, diltiazem) given as an injection into your vein (intravenously) may increase your risk of cardiac arrest.
- inhaled anesthetics used during surgery may further decrease your heart rate
- digitalis glycosides (such as digoxin), used to treat heart failure, may cause an extremely slow heart rate

The following may also interact with APO-METOPROLOL / APO-METOPROLOL (Type L):

- aldesleukin, a medicine used to treat kidney cancer
- alcohol
- medicines that lower blood pressure (e.g. guanethidine, betanidine, reserpine, alpha-methyldopa, clonidine)
- medicines used to treat irregular heartbeat (e.g. quinidine, tocainide, procainamide, ajmaline, amiodarone, flecainide, disopyramide, propafenone, lidocaine)

- medicines used to treat high blood pressure, such as:
  - calcium channel blockers, such as verapamil and diltiazem, taken by mouth
  - hydralazine
  - prazosin
- medicines used to treat high blood pressure in the eye (e.g. timolol)
- MAO Inhibitors
- antidepressants (e.g. fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine)
- antipsychotics (e.g. chlorpromazine, fluphenazine, haloperidol, thioridazine)
- antiretrovirals (e.g. ritonavir)
- antihistamines used to treat hay fever (e.g. diphenhydramine)
- antimalarials (e.g. hydroxychloroquine or quinine)
- antifungals (e.g. terbinafine)
- dipyridamole, used to reduce the risk of blood clots
- ergot alkaloids, used in prevention and treatment of migraine headaches
- fingolimod, a medicine used to treat multiple sclerosis
- rifampicin (an antibiotic)
- anaesthetics, medicines used during surgery (e.g. lidocaine)
- medicines used to treat chest pain (angina) (e.g. nitroglycerin)
- medicines known as non-steroidal anti-inflammatory agents (NSAIDs) used to reduce pain and swelling
- insulin, or oral medicines used to treat high levels of sugar in the blood (diabetes)
- adrenaline or similar substances (sympathomimetics), which are found in some eye and nose drops, and in some cough medicines or remedies for the common cold (e.g. noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives)

How to take APO-METOPROLOL / APO-METOPROLOL (Type L):

Once your healthcare professional has identified the correct dosage for you using the regular metoprolol tartrate tablets, you may be switched to the metoprolol tartrate slow-release tablets. Metoprolol tartrate slow-release tablets are convenient because you only take it once a day.

Take APO-METOPROLOL / APO-METOPROLOL (Type L):

- exactly as your healthcare professional has told you to
- by swallowing the tablet whole
- in the morning, preferably with or right after a meal

Do not change the dose or stop taking APO-METOPROLOL / APO-METOPROLOL (Type L) suddenly without talking to your healthcare professional first. This could cause chest pains or a heart attack. If your healthcare professional decides that you should stop taking APO-METOPROLOL / APO-METOPROLOL (Type L), your dose will be reduced slowly before you stop taking the medicine completely.

Usual dose:

Your healthcare professional will decide how much APO-METOPROLOL / APO-METOPROLOL (Type L) you should take each day depending on your condition.

Depending on how you respond to the treatment, your healthcare professional may change your dose.

The usual adult maintenance doses are:

- To treat high blood pressure: 100 to 200 mg daily. Your healthcare professional may add another medicine such as a diuretic (water pill) for you to take along with APO-METOPROLOL / APO-METOPROLOL (Type L) to treat your high blood pressure.
- To treat chest pain (Angina Pectoris): 200 mg daily.
- To help prevent another heart attack: 100 mg twice daily.

Overdose:

Some of the effects of an overdose of APO-METOPROLOL / APO-METOPROLOL (Type L) are:

- very low blood pressure
- an abnormally slow heartbeat or an irregular heartbeat
- heart failure or stoppage
- sudden and oppressive chest pain (heart attack)
- breathlessness, difficulty breathing when lying down
- low levels of blood sugar
- cardiogenic shock (heart is unable to pump enough blood to the organs of the body)
- loss of consciousness
- seizures
- nausea and vomiting

- blue discoloration of the lips, tongue, skin
- death

Taking APO-METOPROLOL / APO-METOPROLOL (Type L) with alcohol, medicines that lower blood pressure, quinidine, or medicines that have a calming effect on the body (e.g. barbiturates) may make your signs and symptoms worse.

If you think you, or a person you are caring for, have taken too much APO-METOPROLOL / APO-METOPROLOL (Type L), contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using APO-METOPROLOL / APO-METOPROLOL (Type L)?

These are not all the possible side effects you may have when taking APO-METOPROLOL / APO-METOPROLOL (Type L). If you have any side effects not listed here, tell your healthcare professional.

Side effects may include:

- fainting
- dizziness
- light-headedness
- a drop in blood pressure from sitting or standing up
- hot flush
- vivid dreams or nightmares
- headache
- weakness
- sleep disturbance
- fatigue and tiredness especially with activity
- a tingling sensation in the extremities (signs of paresthesia)
- anxiety
- lack of energy and feeling tired (lethargy)
- heartburn
- increased passing of gas
- shortness of breath, especially with exercise
- wheezing
- stuffy or runny nose, sneezing, and itchy nose
- skin rashes

- sweating
- itchy skin
- increased sensitivity of the skin to sun
- hair loss
- muscle spasms
- arthritis
- impotence
- decreased sex drive
- ringing in the ears
- dry, itchy or red eyes
- blurred vision
- increased weight
- confusion
- increased levels of triglycerides (fat) in the blood, and decreased levels of cholesterol

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bradycardia (abnormally slow heartbeat): decreased heart rate that causes you to be dizzy or faint.		√	
Gastrointestinal (GI) problems: constipation, anorexia, abdominal discomfort, indigestion, diarrhea, nausea, or vomiting.		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		√	
Chest Pain		√	
Asthma or bronchospasm (breathing problems): difficulty breathing and coughing, chest tightness, wheezing or whistling sound when breathing.		√	
Congestive heart failure (heart			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
does not pump blood as well as it should): shortness of breath, fatigue, weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, or reduced ability to exercise.			
UNCOMMON			
Edema: ankle swelling.	√		
Slow or irregular heartbeat (palpitations).		√	
New or Worsening Psoriasis: skin rash (in the form of itchy rash, thickened patches of red/silver skin).	√		
Allergic Reaction: rash, swelling of the lips, face or neck, shortness of breath, difficulty speaking, wheezing, drop in blood pressure, feeling sick to your stomach, vomiting, hives, or rash.			√
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain, swelling, nausea, vomiting, unusual dark urine, or unusual tiredness.		√	
Peyronie's disease (a condition where scar tissue forms under the skin of the penis): penile pain, shortening of the penis, erection problems, or significant bend to the penis.		√	
Hallucinations: see or hear things that are not there.		√	
Depression (sad mood that won't go away): difficulty		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive), or thoughts of death or suicide.			
Change in personality and confusion.		√	
Vision changes: blurred vision, loss of vision, or increased sensitivity to light.	√		
Hearing changes: noises, reduced or loss of hearing.	√		
Gangrene: toes or fingers cold to the touch, discoloured and painful.			√
Kidney problems: change in frequency of urination, swelling of extremities, fatigue, skin rash, itching, nausea, vomiting.	√		
Retroperitoneal fibrosis (disorder where there is swelling and scar tissue in back of abdominal cavity): lower back pain, kidney failure (low or no urine produced), high blood pressure, blood clot in the legs.			√
Oculomuco-cutaneous Syndrome (severe skin reaction): red, irritated and watery eyes, skin rash and ear infection.			√
UNKNOWN FREQUENCY			
Heart Block: feeling lightheaded, fainting, dizziness, shortness of breath, nausea or fatigue.			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Raynaud's phenomenon (episodes of reduced blood flow): cold feeling in fingers and toes (and sometimes nose, lips and ears), prickly or stinging feeling, change in skin colour to white then blue.			√
Hepatitis (inflammation of liver): Abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin.			√
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, or weakness.			√
Leukopenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

APO-METOPROLOL / APO-METOPROLOL (Type L): Store at room temperature (15°C to 30°C) and protect from light.

Keep out of reach and sight of children.

If you want more information about APO-METOPROLOL / APO-METOPROLOL (Type L):

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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