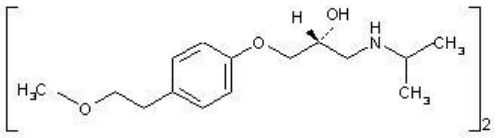
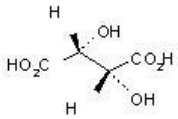
LOPRESOR®
(metoprolol tartrate)

NAME OF THE DRUG

Active ingredient:	metoprolol tartrate
Chemical name:	di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol] L(+)-tartrate
CAS number:	56392-17-7
Molecular weight:	684.81
Molecular formula:	$(C_{15}H_{25}NO_3)_2 \cdot (C_4H_6O_6)$
Chemical structure:	





DESCRIPTION

Metoprolol tartrate is an aryloxypropanolamine derivative. It is a white, odourless or almost odourless, crystalline powder with a melting point of 120^{o}C. It is very soluble in water, soluble in chloroform, methylene chloride and alcohol, and almost insoluble in benzene, diethyl ether and acetone.

Lopresor tablets contain either 50 mg or 100 mg of metoprolol tartrate. They also contain silica-colloidal anhydrous, cellulose - microcrystalline, povidone, sodium starch glycollate, magnesium stearate, hypromellose, and titanium dioxide. The 100 mg strength tablets also contain shellac and indigo carmine CI73015. The 50 mg strength tablets also contain lactose, polysorbate 80, talc - purified, and iron oxide red CI77491

PHARMACOLOGY

Pharmacodynamic properties
Pharmacotherapeutic group: cardio-selective beta-blocker; ATC Code: C07A B02

Mechanism of action (MoA)
Metoprolol, the active substance of Lopresor, is a relatively cardioselective beta-blocker, i.e. it acts on beta$_1$-receptors mainly located in the heart at lower doses than those needed

to influence the $beta_2$-receptors mainly located in the bronchi and peripheral vessels. Metoprolol has little membrane-stabilising effect nor does it display partial agonist activity (i.e. intrinsic sympathomimetic activity = ISA) at doses required to produce beta-blockade.

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 both the standing and lying position. It also reduces the extent of rises in blood pressure occurring in response to physical and mental stress.

In angina pectoris, metoprolol reduces the frequency and severity of the attacks and the need for glyceryl trinitrate relief, and increases exercise tolerance. In cases of supraventricular tachycardia or atrial fibrillation, and in the presence of ventricular extrasystoles, metoprolol has a regulating effect on the heart rate. 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 recurrent myocardial infarction.

Due to its beta-blocking effect, metoprolol is suitable for the prevention of migraine.

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

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

Lopresor has less effect than non-selective beta-blockers on peripheral circulation and the bronchial muscles in therapeutic doses. However, it should be used with caution in patients with asthma, and concomitant use of an adrenergic bronchodilator, e.g. terbutaline or salbutamol, is recommended. Patients already on $beta_2$-stimulants for reversible airways obstruction may require adjustment of dosage if metoprolol therapy is subsequently introduced.

Lopresor inhibits catecholamine-induced lipolysis.

The active metabolite of metoprolol (2-hydroxymetoprolol) does not contribute significantly to the therapeutic effect.

Lopresor is a relatively lipid soluble compound i.e. less soluble than propranolol and more lipid soluble than atenolol.

Based on four studies of metoprolol in healthy males (n=69), the mean maximal β_1 blockade (Emax) measured by reduction in exercise heart rate was 28%, 95% CI [25%, 31%]. The mean metoprolol plasma concentration at 50% of Emax (C_{50}) was 105 nmol/L, 95% CI [74, 135]. β_1 blockade of 30% of maximum was arbitrarily considered the lower limit to obtain a significant effect and was achieved with a mean plasma concentration (C_{30}) of 45 nmol/L, 95% CI [32, 58].

Pharmacokinetics

Absorption:

Metoprolol is rapidly and almost completely (more than 95%) absorbed from the gastro-intestinal tract. Metoprolol exhibits stereo-specific pharmacokinetics.

D**istribution:**

Metoprolol is rapidly and extensively distributed to the extra-vascular tissue. The volume of distribution is 5.6 L/kg. The apparent volume of distribution at steady-state (Vss) in extensive metabolizers (4.84 L/kg) is relatively higher than poor metabolizers (2.83 L/kg). At therapeutic concentrations, approximately 12 % of the active ingredient in Lopresor tablets (metoprolol tartrate) is bound to human serum proteins. Metoprolol crosses the placenta and is found in breast milk (see PRECAUTIONS - Use in Lactation). Metoprolol is not a significant P-glycoprotein substrate indicating that inter-individual variability in pharmacokinetics of metoprolol can be majorly due to CYP2D6 metabolism.

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). There are marked ethnic differences in the prevalence of the poor metabolizers phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolisers. CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizers with normal CYP2D6 activity. Although the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug, caution should be exercised when administering metoprolol to poor metabolisers. Long-term studies have shown that Lopresor neither enhances nor inhibits its own metabolism.

Elimination:

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

a linear relationship to its plasma concentration. The elimination half-life of metoprolol is between 3 and 5 hours. Following single oral administration of 100 mg metoprolol the median clearances were 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultra-rapid metabolizers, respectively. The renal clearance of the stereo-isomers does not exhibit stereo-selectivity in renal excretion.

Dose proportionality

Metoprolol exhibits saturable pre-systemic metabolism leading to non-proportionate increase in the exposure with increased dose.

Food effect

In a study in healthy volunteers (n=8), food significantly increased the extent of absorption of metoprolol after a single 100mg dose ($p<0.05$). The average increase in the plasma-concentration time AUC was 40% (range -28% to 132%). There was considerable variability. There was also a trend to higher and earlier peak plasma concentrations of Metoprolol with food, althought the differences compared with fasting were not significant. It is recommended that Lopresor be taken in standard relation to meals to minimise variations in effects (see "DOSAGE AND ADMINISTRATION").

Dose-response:

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

Pharmacokinetics in the elderly:

The geriatric population may show slightly higher plasma concentrations of metoprolol and the active metabolite alphahydroxymetoprolol than the young as a combined result of a decreased elimination of metoprolol and the metabolite in elderly population and a decreased hepatic blood flow. However, this increase is not clinically significant or therapeutically relevant. Whilst the pharmacokinetics of metoprolol are similar in the young and elderly, there may be pharmacodynamic changes in the elderly such as changes in the number of receptors or decreased receptor sensitivity; therefore, caution in dosing is recommended.

INDICATIONS

- Hypertension: as monotherapy or for use in combination with other antihypertensives.
- Angina pectoris: for long-term prophylaxis. Glyceryl trinitrate should be employed if necessary for alleviating acute attacks.
- Confirmed or suspected myocardial infarction.
- Prevention of migraine.

CONTRAINDICATIONS

- known hypersensitivity to metoprolol and related derivatives

- hypersensitivity to any of the excipients in Lopresor
- sensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur)
- atrioventricular block of second or third degree
- congestive heart failure
- sinus bradycardia (less than 45 to 50 beats/minute)
- sick-sinus syndrome
- severe peripheral arterial circulatory disorders
- shock (including cardiogenic and hypovolaemic shock)
- myocardial infarction patients with a heart rate of < 45 beats/min., a P-R interval of > 0.24 sec., a systolic blood pressure of <100 mm Hg, and/or moderate to severe heart failure
- right ventricular failure secondary to pulmonary hypertension
- significant right ventricular hypertrophy
- hypotension
- untreated phaeochromocytoma (see "PRECAUTIONS")
- allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- severe bronchial asthma or history of severe bronchospasm.

Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients. Therefore, beta-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective beta-blockers can also result in severe bronchospasm. Lopresor should not be used in patients with severe bronchospastic disease (see "PRECAUTIONS").

PRECAUTIONS

Use in Special Patient Groups

Bronchospastic disease:

In general, patients with bronchospastic disease should not be given beta-blockers of any type (e.g. selective or non-selective), including Lopresor. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

Cardiac failure:

Beta-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure are present, the patient should be fully digitalised and/or given a diuretic and carefully monitored. If cardiac failure persists, the beta-blocker should be withdrawn gradually (see statement below regarding abrupt withdrawal).

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

Beta-blockers, including Lopresor, should not be used in patients with untreated congestive heart failure. This condition should first be stabilised.

Myocardial infarction:
In patients with myocardial infarction, if significant hypotension occurs, Lopresor 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.

Prinzmetal angina:
There is a risk of exacerbating the number and duration of coronary artery spasms if patients with Prinzmetal angina or variant angina pectoris are treated with a beta-blocker, including Lopresor. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Conduction disorders:
Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). Lopresor should be administered with caution to patients with first degree A-V block (see "CONTRAINDICATIONS").

Phaeochromocytoma:
In patients known to be, or suspected to be, suffering from a phaeochromocytoma, Lopresor should always be given in combination with an alpha-blocker (e.g. phentolamine or phenoxybenzamine) and only after the alpha blocker has been initiated to avoid exacerbation of hypertension.

Diabetes:
Lopresor should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetic patients should be warned that beta-blockers, including Lopresor, affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

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

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

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

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

Interactions
Calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving Lopresor because there is a risk of cardiac arrest in this situation (see "Interactions with Other Medicines")

Peripheral circulatory disorders:
Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral arterial circulatory disorders (for example, Raynaud's disease or phenomenon, intermittent claudication) (see "CONTRAINDICATIONS").

Renal impairment:

Patients with renal impairment may usually be treated with normal doses. In patients with severe renal disease, haemodynamic changes following beta-blockade may impair renal function further. Caution in Lopresor dosing is recommended in patients with severe renal impairment. There is a possibility of accumulation of one of Lopresor's less active metabolites in patients with a creatinine clearance below 5 mL/min but this accumulation would not influence the beta-blocking properties of metoprolol.

Hepatic impairment:
Metoprolol is mainly eliminated by means of hepatic metabolism (see PHARMACOLOGY - "Pharmacokinetics"). Therefore, hepatic impairment may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma concentrations. Lopressor blood levels are likely to increase substantially

in patients with hepatic impairment. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h), in patients with liver impairment.Therefore, Lopresor should be initiated at low doses with cautious gradual dose titration according to clinical response.

Possible Effects of Treatment:

Effects on the heart rate:
If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/min), the dosage of Lopresor should be gradually reduced or treatment gradually withdrawn (see "CONTRAINDICATIONS").

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

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

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

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

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

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

Driving and using machines

Dizziness, fatigue or visual impairment may occur during treatment with Lopresor (see "ADVERSE EFFECTS"), and may adversely affect the patient's ability to drive or use machinery.

Abrupt withdrawal:

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

Women of child-bearing potential

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

Effects on fertility

The effects of Lopresor on the fertility of humans have not been studied. While metoprolol tartrate showed reversible adverse effects on spermatogenesis (altered morphology and motility) in male rats at less than therapeutic doses, it had no effect on rates of conception in animal fertility studies at up to 11 times the maximum recommended daily dose on a body surface area adjusted basis.

Use in Pregnancy (Category C)

There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly indicated.

Reproduction toxicity studies in mice, rats and rabbits did not indicate teratogenic potential for metoprolol tartarate. Embryotoxicity and/or fetotoxicity in rats and rabbits were noted as increases in preimplantation loss, decreses in the number of viable foetuses per doe, and/or decreses in neonatal survival starting at does of about 300mg/m^2 (on a body surface area adjusted basis), similar to the maximum recommended therapeutic dose. High doses were associated with some maternal toxicity, and growth delay of the offspring in utero, which was reflected in minimally lower weights at birth.

There is a limited amount of data on the use of metoprolol in pregnant women. Experience with metoprolol in the first trimester of pregnancy is limited, but no foetal malformations attributable to metoprolol have been reported.

Beta-blockers may reduce placental perfusion and cause bradycardia in the foetus. During the later stages of pregnancy, these drugs should only be given after weighing the needs of the mother against the risk to the foetus. The lowest possible dose should be used and treatment should be discontinued at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Use in Lactation

The concentration of Metoprolol in breast milk is approximately three times higher than in the mother's plasma. However, in the normal dose range, the amount of metoprolol ingested via human milk seems to be negligible with regard to its beta-blocking effect on the infant. Nevertheless, breast-fed infants should be closely observed for signs or symptoms of beta-blockade.

Use in children:

No paediatric studies have been performed.The safety and efficacy of Lopresor in paediatric patients have not been established.

Use in the elderly:

Caution in dosing is recommended due to increased likelihood of adverse events (see PHARMACOLOGY - PHARMACOKINETICS IN THE ELDERLY).

Genotoxicity

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

INTERACTIONS WITH OTHER MEDICINES

Effect of other medicinal products on metoprolol:

The effects of Lopresor 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.

The following medicinal products may increase the effect or plasma concentrations of metoprolol:

Antiarrhythmic drugs: Beta-blockers may enhance the negative inotropic and negative chronotropic effect of anti-arrhythmic agents of the quinidine type. Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents, disopyramide, procainamide, ajmaline and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone (not available in Australia); the Class III agent, amiodarone; and the Class IV agents (e.g. verapamil). Particularly, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest, and atrioventricular block.

Antihypertensive Drugs: Lopresor enhances the effect of other antihypertensive drugs. The combined effects of Lopresor and other antihypertensive drugs on blood pressure are usually additive.

Calcium antagonists: The concomitant use of beta-blockers and calcium antagonists with myocardial depressant and sinus node activity, e.g. verapamil and to a lesser extent diltiazem, may cause hypotension, bradycardia and asystole. Extreme caution is required if these drugs have to be used together. A calcium channel blocker of the phenylalkylamine type (e.g. verapamil) should not be administered intravenously to patients receiving Lopresor because there is a risk of cardiac arrest in this situation. Concomitant administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium channel blocker of this type in combination with Lopresor should be closely monitored.

The dihydropyridine calcium antagonists (e.g. nifedipine) have a weaker myocardial depressant effect and can be administered cautiously with beta-blockers. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

CYP2D6 Inhibitors: Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metaboliser. Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluvoxamine, fluoxetine, paroxetine, sertraline, bupropion, clomipramine, desipramine antipsychotics such as chlorpromazine, fluphenazine, haloperidol, thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

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

General anaesthetics: 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.

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 post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported.

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.

Glyceryl Trinitrate: Glyceryl Trinitrate may enhance the hypotensive effect of Lopresor.

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

The following medicinal products may decrease the effect or plasma concentration of metoprolol:

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

Hepatic enzyme inducers: Enzyme-inducing drugs may affect plasma concentrations of metoprolol. For example, the plasma concentration of metoprolol is lowered by rifampicin.

Non-steroidal anti-inflammatory drugs: Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker such as indomethacin may decrease the antihypertensive effect of metoprolol, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by non-steroidal anti-inflammatory drugs.

Prazosin: Particular caution is called for when administering a beta-blocker and prazosin together for the first time.

Sympathomimetics: Concomitant administration of sympathomimetic such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, and xanthine derivatives (including, in antitussives or nose and eye drops) may provoke hypertensive reactions when used concomitantly with beta-blockers; however, this is less likely with therapeutic doses of beta1-selective drugs than with non-selective beta-blockers.

A watch should be kept for possible negative inotropic and chronotropic effects when metoprolol is given together with calcium antagonists and/or anti-arrhythmic agents.

Patients receiving concurrent treatment with sympathetic nervous system inhibitors, other beta-blockers (also in the form of eye drops), or MAO inhibitors should be kept under surveillance.

Interactions resulting in effects on other medicines

Alcohol: Metoprolol may modify the pharmacokinetic behaviour of alcohol when taken concomitantly.

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

Anti-adrenergic agents: Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers. Beta- adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia. Concurrent use of beta-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker (the rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a beta-blocker). Furthermore, if both drugs are withdrawn simultaneously, marked rise in blood pressure, and/or arrhythmias may result.

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. When treating diabetics with beta-blockers, caution is indicated and the dosage of antidiabetic medication may need to be adjusted.

Lignocaine: Metoprolol may reduce the clearance of other drugs (e.g. lignocaine, leading to increased ligncaine effects).

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

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.

ADVERSE EFFECTS

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

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

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table Adverse drug reactions from clinical trials

Blood and the lymphatic system disorders	
Rare	agranulocytosis
Very rare	thrombocytopenia
Psychiatric disorders	
Rare	depression, nightmares
Very rare	personality disorder, hallucinations
	mental confusion
Nervous system disorders	
Common	dizziness, headache
Rare	depressed level of consciousness, somnolence or insomnia, paraesthesia
	Short term memory loss
Eye disorders	
Very rare	visual impairment (e.g. blurred vision), dry eyes, eye irritation
Ear and labyrinth disorders	
Very rare	tinnitus, hearing disorders[1] (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	bradycardia
Rare	cardiac failure, arrhythmias, palpitation
Very rare	conduction disorders, precordial pain
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope), peripheral oedema, hypertension (mild and transient), cold extremities, arterial insufficiency
Rare	oedema, Raynaud's phenomenon
Very rare	Gangrene[2]
	angina (mild and transient), intermittent claudication
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, exertional dyspnoea
Rare	Bronchospasm[3]
Very rare	rhinitis
Gastrointestinal disorders	
Common	nausea and vomiting, abdominal pain, heartburn, flatulence, gastric pain

Rare	diarrhoea or constipation
Very rare	dry mouth, retroperitoneal fibrosis (relationship to Lopresor has not been definitely established)
	unstable diabetes

Hepatobiliary disorders

Very rare	Hepatitis

Skin and subcutaneous tissue disorders

Common	pruritis, rash
Rare	rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	Photosensitivity reaction, hyperhydrosis, reversible alopecia, worsening of psoriasis
	sweating increased

Musculoskeletal, connective tissue disorders

Rare	muscle spasms
Very rare	arthritis
	muscoskeletal pain

Reproductive system and breast disorders

Very rare	erectile dysfunction ,libido disorder and potency, Peyronie's disease[4]

Immune system disorders

	hypersensitivity

General disorders and administration site conditions

Common	fatigue
	tiredness

Investigations

Very rare	weight gain, liver function test abnormal

[1]in doses exceeding those recommended
[2]in patients with pre-existing severe peripheral circulatory disorders
[3]which may occur in patients without a history of obstructive lung disease
[4]relationship to Lopresor has not been definitely established

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

The oculomucocutaneous syndrome associated with the beta-blocker, practolol, has not been reported with Lopresor (see “PRECAUTIONS”).

Post-marketing Data - Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse reactions have been derived from post-marketing experience with Lopresor via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Nervous system disorders:
confusional state

Investigations:
increase in blood triglycerides, decrease in high density lipoprotein (HDL)

Potential Adverse Reactions

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

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

DOSAGE AND ADMINISTRATION

Dosage
The maximum daily dose should not exceed 400 mg.

Although twice daily dosage is optimal, in those patients whose maintenance dosage is

150 mg daily or less, it may be administered as a single dose.

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

Hypertension:	
Mild:	50 or 100 mg, given once daily for one week
Moderate to severe:	50 or 100 mg, given twice daily for one week
Maintenance:	50 or 100 mg, given once or twice daily. Some patients may respond to 50 mg. A larger number will respond to 100 mg, given once daily as initial and maintenance therapy. Response is rarely improved by increasing the dose beyond 200 mg daily
Angina pectoris:	50 mg to 100 mg, given two or three times daily
Myocardial infarction:	The recommended dosage can be reduced depending on the haemodynamic status of the patient. Initially, therapy should commence with 50 mg twice daily and be continued for 48 hours
Maintenance:	generally 100 mg, given twice daily
Prevention of migraine:	100 to 150 mg, given in two divided doses (morning and evening)

Method of Administration
The film coated tablets should be swallowed whole with a glass of water.

Lopresor should always be taken in standard relation to meals. For example, if it is decided that the patient should take Lopresor with breakfast, the patient should continue to take it with breakfast throughout the course of therapy.

OVERDOSAGE

Signs and symptoms:
An overdosage of Lopresor 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 aggravate the signs and symptoms.

The first manifestations of overdosage can appear in 20 minutes but are more commonly seen within 1 to 2 hours after the drug's ingestion. The effects of massive overdosage may persist for several days despite declining plasma concentrations.

Treatment:
Contact the Poisons Information Centre on 131 126 for advice on management.

Patients suffering from overdosage of a beta-blocker should always be hospitalised so that vital functions can be monitored. In general, patients with acute or recent myocardial infarction may be more haemodynamically unstable than other patients and should be treated accordingly. Induction of vomiting or gastric lavage should be undertaken.

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

In the presence of severe hypotension, bradycardia, and impending heart failure, administer a $beta_1$-stimulant (e.g. isoprenaline) intravenously at 2 to 5 minute intervals until the desired effect is achieved. Where a $beta_1$-stimulant is not available, administer 0.5 to 2.0 mg atropine sulphate i.v. in order to block the vagus nerve. If a satisfactory effect is not achieved, agents such as dopamine, dobutamine, or noradrenaline may be administered.

Further measures: 1 to 5 (max 10) mg glucagon (glucagon activates the adenylcyclase system independently of the beta-receptor, augmenting contractility in the presence of beta-blockade); transvenous intracardiac pacemaker. To combat bronchospasm, a $beta_2$-stimulant (e.g. salbutamol) or aminophylline can be given. i.v.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Tablets 50mg: rose pink, heart-shaped, film-coated, marked HM, CIBA on reverse; bottle pack of 100's.

Tablets 100mg: light blue, heart-shaped, film-coated, scored, marked IP, CIBA on reverse; bottle pack of 60's.

Storage:
Store below 30°C. Protect from moisture. Keep out of reach of children.

Poisons schedule:

Prescription Only Medicine (S4)

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113
Telephone: (02) 9805 3555
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