**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$_3$)$_2$.(C$_4$H$_6$O$_6$)

**DESCRIPTION**

Metoprolol tartrate is an aryloxypropanolamine derivative. It is a white, odourless or almost odourless, crystalline powder with a melting point of 120$^\circ$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 beta₂-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 beta₂-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.
Pharmacokinetics

Absorption:
Metoprolol is rapidly and almost completely (more than 95%) absorbed from the gastrointestinal tract.

Distribution:
Metoprolol is rapidly and extensively distributed to the extra-vascular tissue. The volume of distribution is 5.6 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).

Metabolism:
Metoprolol 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). 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.

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:
Elderly subjects showed no significant differences in the plasma concentrations of metoprolol as compared with young persons, in a study involving eight healthy elderly individuals (mean age 74.5 years) and eight young subjects (mean age 26.3 years).
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 atroventricular 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:**
Where Lopresor is prescribed for a patient known to be, or suspected to be, suffering from a phaeochromocytoma, an alpha-blocker (e.g. phentolamine or phenoxybenzamine) should be administered before the beta-blocker 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 vascular disease:**
Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of
peripheral vascular disease (see “CONTRAINDICATIONS”).

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

Use in children:
The safety and efficacy in children have not been established.

Use in the elderly:
Caution is indicated in elderly patients. An excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

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), or monoamine oxidase (MAO) inhibitors, should be carefully monitored.

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 atroventricular 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.

**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:** Anti-hypertensive 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 lignocaine 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.
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-adrenoeceptors 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, pratolol, 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 pratolol syndrome. On a few rare occasions, serous otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported.

The full oculomucocutaneous syndrome as reported with pratolol and some other beta-blockers 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.

Use in Pregnancy (Category C)
Lopresor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the foetus when Lopresor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

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.

Experience with metoprolol in the first trimester of pregnancy is limited, but no foetal malformations attributable to metoprolol have been reported. In general, no drug should be taken during the first 3 months of pregnancy, and the relative benefits and risks of treatment should be carefully considered throughout pregnancy.

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
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.

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:

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Lopresor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (systolic BP &lt; 90 mmHg)</td>
<td>27.4%</td>
<td>23.2%</td>
</tr>
<tr>
<td>Bradycardia (heart rate &lt; 40 beats/min)</td>
<td>15.9%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Second- or third-degree heart block</td>
<td>4.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>First-degree heart block (P-R &gt; 0.26 sec)</td>
<td>5.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>27.5%</td>
<td>29.6%</td>
</tr>
</tbody>
</table>

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

Immune system disorders
hypersensitivity

General disorders and administration site conditions
Common fatigue
tiredness

Investigations
Very rare weight gain, liver function test abnormal

Post-marketing Data
In addition to the adverse events reported in the clinical trials, the following events have been reported during post-marketing surveillance of Lopresor*:

Nervous system disorders:
confusional state

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

\(^1\) 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
In addition to the adverse events reported in the clinical trials, the following events have been reported during post-marketing surveillance of Lopresor*:
* Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

**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.

It is advisable to individualise the dosage.

**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 generally 100 mg, given twice daily

**Maintenance:**

**Prevention of migraine:**

100 to 150 mg, given in two divided doses (morning and evening)

**Administration**
The film coated tablets should be swallowed whole.

**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.

In the presence of severe hypotension, bradycardia, and impending heart failure, administer a beta₁-stimulant (e.g. isoprenaline) intravenously at 2 to 5 minute intervals until the desired effect is achieved. Where a beta₁-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 beta₂-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

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