

Drug Regulatory Affairs

LOPRESOR[®] / LOPRESOR[®] RETARD
(metoprolol tartrate)

Ampoules (5 mL) of 5 mg
50 mg or 100 mg tablets
100 mg or 200 mg sustained-release tablets (Divitabs)

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

LOPRESOR®

LOPRESOR® RETARD

2 Qualitative and quantitative composition

The active ingredient is Di-[(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol] L(+)-tartrate (metoprolol tartrate).

Metoprolol is an aryloxypropanolamine derivative.

One ampoule contains 5 mg metoprolol tartrate. One tablet contains 50 mg, 100 mg or 200 mg metoprolol tartrate.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Lopresor®

Ampoules (5 mL) of 5 mg

Tablets of 50 mg and 100 mg

Lopresor® Retard

Sustained-release tablets of 100 mg and 200 mg

Divitabs (fractionable sustained-release tablets) of 200 mg

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

All forms

Disturbances of cardiac rhythm, including supraventricular and ventricular arrhythmias.

Confirmed or suspected acute myocardial infarction, for secondary prevention after myocardial infarction.

Oral forms only

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

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

Hyperthyroidism (as adjunctive medication).

Functional heart disorders with palpitation.

Prevention of migraine.

4.2 Posology and method of administration

Parenteral administration of Lopresor should be supervised by experienced staff in a setting in which monitoring and resuscitating equipment are available. For oral treatment, the tablets should be swallowed unchewed.

It is advisable to individualise the dosage. The following dosage recommendations may be taken as a guide:

Disturbances of cardiac rhythm

Ampoules: Initially up to 5 mg, injected slowly intravenously (1 to 2 mg/min). The injection can be repeated at 5-minute intervals until a satisfactory response has been obtained. A total dose of 10 to 15 mg generally proves sufficient; increasing the dose to 20 mg or more does not usually yield better results.

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

Myocardial infarction

The recommended dosage can be reduced depending on the haemodynamic status of the patient.

a) Treatment in the acute stage

Lopresor should be administered as soon as possible after the patient's arrival in hospital. Under constant haemodynamic monitoring (ECG, blood pressure, heart rate) one 5-mg bolus injection should be given intravenously, and repeated at 2-minute intervals up to a total dose of 15 mg. Should any of the conditions listed under "Contraindications" arise, intravenous administration should be stopped immediately and appropriate measures instituted (see also section 4.9. Overdose). Provided the full intravenous dose (15 mg) has been well tolerated, oral therapy should be started 15 minutes later with 50 mg every 6 hours for 48 hours. For patients who do not tolerate the full intravenous dose, oral therapy should be cautiously initiated, starting with half the aforementioned oral dose.

b) Maintenance treatment

The oral maintenance dose is 200 mg daily, given in 2 divided doses. The treatment should be continued for at least 3 months.

Hypertension

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

Divitabs (fractionable sustained-release tablets): 1 of the Divitabs early in the morning. If necessary, another antihypertensive can be prescribed in addition. In mild hypertension, ½ of one of the Divitabs taken early in the morning may suffice.

Angina pectoris

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

Divitabs: ½ or 1 of the Divitabs early in the morning; if necessary, this dose can be repeated in the evening.

Hyperthyroidism

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

Functional heart disorders with palpitation; prevention of migraine

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

Divitabs: ½ of one of the Divitabs daily, given in the morning; if necessary, the daily dosage can be raised to 1 of the Divitabs, to be taken also as a single dose in the morning.

Children

The safety and efficacy of Lopresor and Lopresor Retard in children have not been established.

4.3 Contraindications

Known hypersensitivity to metoprolol and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur).

Atrioventricular block of second or third degree.

Decompensated heart failure.

Clinically relevant sinus bradycardia (heart rate less than 45 to 50 beats/min).

Sick-sinus syndrome.

Severe peripheral arterial circulatory disorders.

Cardiogenic shock.

Untreated phaeochromocytoma (see section 4.4. Special warnings and precautions for use).

Hypotension.

For oral use: severe bronchial asthma or history of severe bronchospasm.

For intravenous use: bronchial asthma and history of bronchospasm (see section 4.4. Special warnings and precautions for use).

Use of Lopresor is contraindicated in patients with myocardial infarction who have a heart rate of less than 45 to 50 beats/min, P-R interval of greater than 0.24 sec, a systolic blood pressure of less than 100 mmHg, and/or severe heart failure.

4.4 Special warnings and precautions for use

In general, patients with bronchospastic diseases should not be given beta-blockers, including Lopresor. However, because of its relative cardioselectivity, oral Lopresor may be administered with caution to patients with mild or moderate bronchospastic diseases who do

not respond to, or cannot tolerate, other suitable treatments. Since β_1 -selectivity is not absolute, a β_2 -agonist should be administered concomitantly, and the lowest possible dose of Lopresor should be used.

Lopresor should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents (see section 4.5. Interaction with other medicinal products and other forms of interaction). Diabetic patients should be warned that beta-blockers, including Lopresor, may mask the tachycardia occurring with hypoglycaemia; however, other manifestations of hypoglycaemia such as dizziness and sweating may not be significantly suppressed, and sweating may be increased.

Beta-blockers, including Lopresor, should not be used in patients with untreated congestive heart failure (see section 4.3. Contraindications). This condition should first be stabilised.

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

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

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

In patients known to have, or suspected of having, a phaeochromocytoma, Lopresor should always be given in combination with an alpha-blocker (see section 4.3. Contraindications).

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

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

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

Lopresor treatment should not be stopped suddenly, especially in patients with ischaemic heart disease. To prevent exacerbation of angina pectoris, the dosage should be gradually reduced over 1 to 3 weeks and, if necessary, replacement therapy should be initiated at the same time.

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers, including Lopresor, should be avoided for patients who are at increased risk of anaphylaxis.

Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). Relatively selective beta₁-receptor blockers, such as Lopresor, can be used in such patients, but only with the utmost care.

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, where Lopresor is administered to patients having, or suspected of developing, thyrotoxicosis, both thyroid and cardiac function should be monitored closely.

The full oculomucocutaneous syndrome, as described elsewhere with practolol, has not been reported with Lopresor. However, part of this 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on metoprolol

The effects of Lopresor or Lopresor Retard 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

Calcium channel 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 Lopresor because there is a risk of cardiac arrest in this situation. Patients taking an oral calcium channel blocker of the verapamil type in combination with Lopresor should be closely monitored.

Class I anti-arrhythmic drugs and amiodarone

Amiodarone, propafenone, and other class I anti-arrhythmic agents such as quinidine and disopyramide may potentiate the effects of beta-blockers on heart rate and atrioventricular conduction.

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of Lopresor.

General anaesthetics

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

CYP2D6 inhibitors

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer (phenocopying, see section 5.2. Pharmacokinetic properties). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as 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.

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

Prazosin

The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker.

Digitalis glycosides

Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time.

Sympathomimetics

Adrenaline or other sympathomimetic agents (for example, 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.

Non-steroidal anti-inflammatory drugs

Concurrent treatment with non-steroidal anti-inflammatory drugs such as indomethacin may decrease the antihypertensive effect of metoprolol.

Hepatic enzyme inducers

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

Effect of metoprolol on other medicinal products

Clonidine

If a patient is treated with clonidine and Lopresor concurrently, and clonidine treatment is to be discontinued, Lopresor should be stopped several days before clonidine is withdrawn. This is because the hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Insulin and oral hypoglycaemic drugs

In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a beta₁-selective drug such as Lopresor than with a non-selective beta-blocker. However, diabetic patients receiving Lopresor should

be monitored to ensure that diabetes control is maintained (see also section 4.4. Special warnings and precautions for use).

Lidocaine (xylocaine)

Metoprolol may reduce the clearance of lidocaine, leading to increased lidocaine effects.

Alcohol

Metoprolol may modify the pharmacokinetic parameters of alcohol.

4.6 Pregnancy and lactation

Pregnancy

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.

Experience with metoprolol in the first trimester of pregnancy is limited, but no fetal malformations attributable to metoprolol have been reported. However, beta-blockers may reduce placental perfusion. The lowest possible dose should be used, and treatment should be discontinued at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn baby (for example, bradycardia, hypoglycaemia).

Lactation

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

4.7 Effects on ability to drive and use machines

Lopresor may cause dizziness, fatigue or visual disturbances (see section 4.8. Undesirable effects), and therefore may adversely affect the patient's ability to drive or use machines.

4.8 Undesirable effects

Frequency estimates: very common $\geq 10\%$; common $\geq 1\%$ and $< 10\%$; uncommon $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare $< 0.01\%$.

Blood and the lymphatic system disorders

Very rare thrombocytopenia

Psychiatric disorders

Rare depression, nightmares

Very rare personality disorder, hallucinations

Nervous system disorders

Common dizziness, headache

Rare alertness decreased, somnolence or insomnia, paraesthesia

Eye disorders

Very rare visual disturbance (e.g. blurred vision), dry eyes and/or eye irritation

Ear and labyrinth disorders

Very rare tinnitus, and, in doses exceeding those recommended, hearing

	disorders (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	bradycardia
Rare	heart failure, cardiac arrhythmias, palpitation
Very rare	cardiac conduction disorders, precordial pain,
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope)
Rare	oedema, Raynaud's phenomenon
Very rare	gangrene in patients with pre-existing severe peripheral circulatory disorders
Respiratory, thoracic and mediastinal disorders	
Common	exertional dyspnoea
Rare	bronchospasm (which may occur in patients without a history of obstructive lung disease)
Very rare	rhinitis
Gastrointestinal disorders	
Common	nausea and vomiting, abdominal pain
Rare	diarrhoea or constipation
Very rare	dry mouth, retroperitoneal fibrosis (relationship to Lopresor has not been definitely established).
Hepatobiliary disorders	
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Rare	skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis.
Musculoskeletal, connective tissue disorders	
Rare	muscle cramps
Very rare	arthritis,
Reproductive system and breast disorders	
Very rare	disturbances of libido and potency, Peyronie's disease (relationship to Lopresor has not been definitely established)
General disorders and administration site conditions	
Common	Fatigue
Investigations	
Very rare	Weight increase, liver function test abnormal

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of Lopresor: Confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). 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.

4.9 Overdose

Signs and symptoms

Poisoning due to an overdose of Lopresor may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness (or even coma), convulsions, nausea, vomiting, and cyanosis.

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

The first manifestations of overdose appear 20 minutes to 2 hours after ingestion of Lopresor. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Treatment

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

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

Atropine may be given intravenously to control significant bradycardia. Intravenous beta-agonists such as prenalterol or isoprenaline should be used to treat bradycardia and hypotension; very high doses may be needed to overcome the beta-blockade. Dopamine, dobutamine or noradrenaline may be given to maintain blood pressure. Glucagon has positive inotropic and chronotropic effects on the heart that are independent of beta-adrenergic receptors, and has proved effective in the treatment of resistant hypotension and heart failure associated with beta-blocker overdose.

Diazepam is the drug of choice for controlling seizures. A beta-agonist or aminophylline can be used to reverse bronchospasm; patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

The beta-blocker withdrawal phenomenon (see section 4.4. Special warnings and precautions for use) may occur after overdose.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Pharmacotherapeutic group: Cardioselective beta-blocker, ATC code: C07A B02

Pharmacodynamic effects and mechanism of action

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

The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility, and cardiac output.

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

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

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

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

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

Long-term treatment with metoprolol may reduce insulin sensitivity. However, metoprolol interferes with insulin release and carbohydrate metabolism less than non-selective beta-blockers.

In short-term studies it has been shown that metoprolol may alter the blood lipid profile. It may cause an increase in triglycerides and a decrease in free fatty acids; in some cases, a small decrease in the high-density lipoprotein (HDL) fraction has been observed, although to a lesser extent than with non-selective beta-blockers. In one long-term study lasting several years, cholesterol levels were found to be reduced.

5.2 Pharmacokinetic properties

Absorption

Metoprolol is absorbed from all parts of the intestine. After dosing with the conventional tablets, absorption is rapid and complete. With Lopresor Retard tablets, absorption is slower, but the availability of metoprolol is similar compared with conventional tablets. Peak plasma concentrations are attained after approximately 1.5 to 2 hours with conventional metoprolol tablets, and after approximately 4 to 5 hours with sustained-release tablets. Plasma concentrations of metoprolol increase approximately in proportion with the dose in the 50-mg to 200-mg dose range. Owing to extensive hepatic first-pass metabolism, approximately 50% of a single oral dose of metoprolol reaches the systemic circulation. The extent of presystemic elimination differs between individuals because of genetic differences in oxidative metabolism. Although the plasma profiles exhibit wide intersubject variability, they are reproducible within an individual. Upon repeated administration, the percentage of the dose systemically available is approximately 40% higher than after a single dose (that is,

approximately 70%). This may be due to partial saturation of the first-pass metabolism, or reduced clearance as a result of reduced hepatic blood flow. Ingestion with food may increase the systemic availability of a single oral dose by approximately 20% to 40%.

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

Distribution

Metoprolol is rapidly distributed, with a reported volume of distribution of 3.2 to 5.6 L/kg. The half-life is not dose-dependent and does not change on repeated dosing. Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk (see section 4.6. Pregnancy and lactation). In patients with hypertension, metoprolol concentrations in cerebrospinal fluid are similar to those in plasma.

Biotransformation

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 (PM) phenotype. Approximately 7% of Caucasians and less than 1% Orientals are PMs.

CYP2D6 poor metabolisers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolisers with normal CYP2D6 activity. However, the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol contribute significantly to its beta-blocking effect.

Elimination

The average elimination half-life of metoprolol is 3 to 4 hours; in poor metabolisers the half-life may be 7 to 9 hours. Approximately 95% of the dose can be recovered in urine. In most subjects (extensive metabolisers), less than 5% of an oral dose, and less than 10% of an intravenous dose, is excreted as unchanged drug. In poor metabolisers, up to 30% or 40% of oral or intravenous doses, respectively, may be excreted unchanged. The total plasma clearance of metoprolol after intravenous administration is approximately 1 L/min.

Characteristics in patients

Elderly subjects show no significant changes in the plasma concentrations of metoprolol as compared with young persons.

Impaired renal function has no influence on the bioavailability of metoprolol or on its elimination. The excretion of metabolites, however, is reduced. Significant accumulation of metabolites will occur only in patients with a creatinine clearance of approximately 5 mL/min or less, and this accumulation would not influence the beta-blocking properties of metoprolol.

Liver cirrhosis may increase the bioavailability of unchanged metoprolol and reduce its total clearance.

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

Inflammatory disease has no effect on the pharmacokinetics of metoprolol. Hyperthyroidism may increase the presystemic clearance of metoprolol.

5.3 Preclinical safety data

Reproductive toxicity

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

Mutagenicity

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

Carcinogenicity

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

6 Pharmaceutical particulars

6.1 List of excipients

Lopresor

Solution for injection: Sodium chloride, water for injection.

Tablets of 50 mg (F52): Silica aerogel, cellulose, lactose, magnesium stearate, sodium carboxymethyl starch, hydroxypropyl methylcellulose, red iron oxide (E 172), polysorbate 80, talc, titanium dioxide (E 171).

Tablets of 50 mg (F7): Silica aerogel, cellulose, lactose, magnesium stearate, polyvinylpyrrolidone, sodium carboxymethyl starch, hydroxypropyl methylcellulose, red iron oxide (E 172), polysorbate 80, talc, titanium dioxide (E 171).

Tablets of 100 mg: Silica aerogel, cellulose, magnesium stearate, sodium carboxymethyl starch, hydroxypropyl methylcellulose, glyceryl polyethylene glycol oxystearate, talc, titanium dioxide (E 171).

Lopresor Retard

Sustained-release tablets of 100 mg and 200 mg: Silica aerogel, cellulose, dibasic calcium phosphate, hydrogenated castor oil, copolymer based on polyacrylic/methacrylic esters, magnesium stearate, hydroxypropyl methylcellulose, yellow iron oxide (E 172), polysorbate 80, talc, titanium dioxide (E 171).

Divitabs (divisible sustained-release tablets) of 200 mg: Silica aerogel, cellulose, dibasic calcium phosphate, copolymer based on polyacrylic/methacrylic esters, magnesium stearate, hydroxypropyl methylcellulose, glycol palmitostearate, yellow iron oxide (E 172), polysorbate 80, talc, titanium dioxide (E 171).

Information might differ in some countries.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Lopresor, Lopresor Retard

Ampoules: 5 years

Tablets of 50 mg and 100 mg: 5 years

Lopresor Retard

Sustained-release tablets of 100 mg: 3 years

Sustained-release tablets of 200 mg: 5 years

Divitabs of 200 mg: 5 years

Information might differ in some countries.

6.4 Special precautions for storage

Lopresor, Lopresor Retard

Ampoules: Protect from light.

Tablets of 50 mg: Protect from moisture and heat (store below 30°C).

Tablets of 100 mg: Protect from moisture.

Lopresor and Lopresor Retard should be kept out of the reach and sight of children.

Information might differ in some countries.

6.5 Nature and contents of container

Information might differ in some countries.

6.6 Instructions for use and handling

There are no specific instructions for use/handling.