

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metocor 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg metoprolol tartrate.
Excipients: Contains Lactose Monohydrate 49.75mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, round biconvex tablets with a score notch on one side.

The scoreline allows the tablet to be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metocor is indicated for hypertension and angina pectoris and as adjunct to the treatment of thyrotoxicosis.

Metocor is indicated for the treatment of Cardiac arrhythmias, especially supraventricular tachyarrhythmias.

Metocor has been shown to reduce mortality when administered to patients with definite or suspected acute myocardial infarction.

Metocor is also indicated in the prophylaxis of migraine.

4.2 Posology and method of administration

Route of Administration: Oral.

The dose must always be adjusted to the individual requirements of the patient but should not exceed 400 mg/day. The following are guidelines:

Recommended Dosage Schedule: Adults only.

Hypertension: Initially a dose of 100 mg in the morning should be prescribed. Depending upon the response the dosage may be increased to 200 mg daily given in single or divided doses. Up to 400mg daily may be given. Over the dosage range most patients may be expected to respond rapidly and satisfactorily. A further reduction in blood pressure may be achieved if Metocor is used in conjunction with an antihypertensive diuretic such as Chlorthalidone or a vasodilator such as hydralazine.

Metocor may be administered with benefit both to previously untreated patients with hypertension and in those in whom the response to previous therapy is inadequate. In the latter type of patient the previous therapy may be continued and Metocor added in to the regime with adjustment of the previous therapy if necessary.

Angina pectoris: 50 – 100 mg, twice or three times daily.

In general a significant improvement in exercise tolerance and reduction of anginal attacks may be expected with a dose of 50–100 mg twice daily.

Cardiac Arrhythmias: A dose of 50 mg two or three times daily is usually sufficient. If necessary the dose can be increased up to 300 mg per day administered in divided doses.

Following the treatment of an acute arrhythmia with Metoprolol injection continuation therapy with Metocor tablets should be initiated 4 – 6 hours later. In such cases, the initial dose should not exceed 50 mg three times daily.

Thyrotoxicosis: 50 mg four times daily.

Myocardial Infarction: Early intervention. Oral therapy should commence fifteen minutes after the last metoprolol injection with 50 mg every six hours for forty eight hours. Patients who fail to tolerate the full intravenous dose should have their oral therapy initiated with caution. It is suggested that half the oral dose may be appropriate.

Prophylaxis after myocardial infarction:

Maintenance dose is 100 mg twice daily.

If it becomes necessary to discontinue treatment with a beta-blocker one should withdraw the drug gradually, i.e. over a period of 8-10 days because abrupt interruption of the medication particularly in cases of ischaemic heart disease – may be followed by an acute deterioration in the patient's condition.

Prophylaxis of Migraine: 100-200 mg in divided doses [morning and evening].

Patients with renal impairment

The rate of elimination is insignificantly affected by renal function and therefore no dose adjustment is needed.

Patients with hepatic impairment

Usually metoprolol can be given at the same dose to patients with cirrhosis of the liver as to patients with normal hepatic function. A dose reduction should only be considered when there are signs of severely impaired hepatic function (i.e. shunt operated patients) (see Section 5.2).

Elderly patients

There are no adequate data from the use in patients above the age of 80. Take special precautions when increasing the dose. However, caution is advised in elderly patients as a fall in blood pressure or excessive bradycardia may have more pronounced effects.

Paediatric population:

There is limited data on the use of metoprolol in children and adolescents, therefore the use of metoprolol is not recommended.

Method of administration

The tablets should be taken preferably with breakfast (see section 5.2).

4.3 Contraindications

Metocor is contra-indicated in patients with:

- Hypersensitivity to metoprolol, other beta blockers or to any of the excipients listed in Sec 6.1.
- Grade II or III atrioventricular block.
- Unstable or acute decompensated heart failure (pulmonary oedema, hypoperfusion or hypotension), in which case continuous or periodical intravenous inotropic β receptor agonist therapy is indicated.
- Manifest and clinically significant bradycardia (heart frequency < 50/min.).
- Cardiogenic shock.
- Sick-sinus syndrome.
- Severe peripheral arterial disease.

- Systolic hypotension.
- Severe bronchial asthma or chronic obstructive pulmonary disease.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Higher grade sinoatrial block.

Metoprolol may not be administered to patients with suspected acute myocardial infarction and a heart rate of < 50 beats/min., PQ interval > 0.24 seconds or systolic blood pressure < 100 mmHg

Like other beta-blockers, Metocor should not be given in combination with anti-arrhythmic agents of the verapamil type because their concomitant use may result in bradycardia, hypotension or even cardiac arrest.

4.4 Special warnings and precautions for use

Although it is a selective beta-blocker it is prudent to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Metocor can be administered with caution to patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the β -blocker, depending on the degree of airways resistance and the benefit derived from β -blockade. Beta blockers must be administered with caution to asthmatics.

If an asthmatic uses a beta-2 agonist (as tablets or by inhalation) when initiating metoprolol treatment, the dose of the beta-2 agonist must be controlled and increased if necessary.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia.

Metoprolol may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse. AV conduction disorders may be aggravated in rare cases in connection with metoprolol treatment (possible atrioventricular block). Beta-blockers should be given only with caution to patients with first degree atrioventricular block (see section 4.3).

In the case of increasing bradycardia the dosage should be reduced, or treatment gradually discontinued. Beta blocker treatment must not be suddenly discontinued. If the treatment is to be discontinued, it must, where possible, be gradually reduced over a period of at least two weeks during which the dose is withdrawn gradually, the doses diminishing to 25 mg for the last 6 days before the treatment is discontinued. If the patient presents with any symptoms, the dose should be reduced at a lower rate. Sudden discontinuation of beta blockers may possibly exacerbate heart failure and increase the risk of myocardial infarction and sudden death.

Metoprolol may exacerbate the symptoms of peripheral vascular disorders due to its antihypertensive effect.

In patients with Prinzmetal's angina β_1 selective agents should be used with care because may increase the number and duration of angina attacks.

Metoprolol treatment may possibly mask the symptoms of thyrotoxicosis. Therefore, metoprolol should be administered with caution to patients having or suspected of developing thyrotoxicosis and both thyroid and cardiac functions should be monitored closely.

Before surgery, the anaesthesiologist must be informed that the patient takes beta blockers. It is not recommended to discontinue beta blocker treatment during a surgical procedure.

Beta blockers may trigger or exacerbate psoriasis.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn.

Discontinuation of the beta-adrenoceptor blocking drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-blocker should be gradual.

Like other beta blockers, metoprolol may also increase both the sensitivity to allergens and the severity of anaphylactic reactions. Adrenalin treatment does not always give the desired therapeutic effect in individuals receiving beta blockers (see also section 4.5).

In patients with pheochromocytoma they should be treated with an alpha-blocker beforehand.

Up to the present, there is insufficient data from the use of metoprolol in patients with heart failure and the following accompanying factors:

- Unstable heart failure (NYHA IV).
- Acute myocardial infarction or unstable angina pectoris in the preceding 28 days.
- Impaired renal function.
- Impaired hepatic function.
- Patients above the age of 80.
- Patients under the age of 40.
- Haemodynamically significant valve diseases.
- Hypertrophic obstructive cardiomyopathy.
- During or after cardiac surgery within the last four months before treatment with metoprolol.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with metoprolol should be avoided:

Barbituric acid derivatives

Barbiturates (e.g. pentobarbital) induce the metabolism of metoprolol through enzyme induction.

Propafenone

When propafenone was commenced in four patients, who were then treated with metoprolol, the plasma concentrations of metoprolol increased 2-5-fold and two patients suffered typical metoprolol side effects. The interaction was confirmed in a study involving eight healthy research subjects. The interaction is probably due to the fact that propafenone like quinidine, inhibits the metabolism of metoprolol via cytochrome P450 2D6. The combination is probably difficult to manage due to the fact that propafenone also has beta-receptor blocking properties.

Calcium antagonists

In the case of the concomitant use of calcium antagonists of the verapamil or diltiazem types, an increase in negative inotropic and chronotropic effects can occur. Calcium antagonists of the verapamil type should not be administered intravenously to patients who are being treated with beta blockers, due to the risk of hypotension, AV conduction disturbances, and left ventricular insufficiency (see section 4.3). In patients with impaired cardiac function, the combination is contraindicated. As with other beta-blockers, concomitant therapy with dihydropyridines (such as nifedipine and amlodipine), may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

The following combinations with metoprolol may require dose adjustment.

Amiodarone

One case history indicates that patients treated with amiodarone can develop severe sinus bradycardia during concomitant treatment with metoprolol. Amiodarone has an extremely long half-life (approximately 50 days), which means that interactions can occur a long time after discontinuation of the preparation.

Class I-antiarrhythmics

Class I-antiarrhythmics and beta-receptor blockers have additive negative inotropic effects, which can result in serious haemodynamic adverse reactions in patients with impaired left-ventricular function. The combination should be avoided in “sick sinus syndrome” and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory drugs/antirheumatic agents (NSAID)

NSAID-type antiphlogistics counteract the antihypertensive effect of beta-receptor blocking agents. Studies have primarily been performed on indomethacin. It has not been possible to demonstrate such an interaction in a study relating to diclofenac.

CYP2D6 inhibitors

Metoprolol is a CYP2D6-substrate. Drugs which inhibit this enzyme may increase the plasma concentration of metoprolol. Examples of clinically significant inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as quinidine, 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. On commencement of treatment with these medicinal products in patients being treated with metoprolol the dose of metoprolol may need to be reduced.

Diphenhydramine

Diphenhydramine reduces (2.5 times) clearance of metoprolol to alpha-hydroxymetoprolol in fast hydroxylators via CYP 2 D6, at the same time as the effects of metoprolol are increased.

Digitalis glycosides

Digitalis glycosides in connection with beta-receptor blockers, can increase the atrioventricular conduction time and induce bradycardia.

Epinephrine

A dozen reports exist in respect of severe hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propranolol), who were administered epinephrine (adrenaline). These clinical observations have been confirmed in studies on healthy research subjects. It has also been suggested that epinephrine, administered as local anaesthesia, may give rise to these reactions on intravascular administration. The risk should be considerably less with cardioselective beta-receptor blockers.

Phenylpropanolamine

Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological levels in healthy research subjects. In general, propranolol counteracts the rise in blood pressure triggered by phenylpropanolamine. Beta-receptor blockers may, however, trigger paradoxical hypertensive reactions in patients taking high doses of phenylpropanolamine. Hypertensive crises during treatment solely with phenylpropanolamine have been described in a couple of cases.

Quinidine

Quinidine inhibits the metabolism of metoprolol in so-called “fast hydroxylators” with significantly increased plasma values and resultant increase in beta blockade. Similar reaction might be expected to occur with other beta-blockers which are metabolized by the same enzyme (cytochrome P450 2 D6).

Sympathetic ganglion blockers or other beta blockers

Patients who are concomitantly receiving sympathetic ganglion blockers, or other beta blockers (including in the form of eye drops) must continue being monitored.

MAO inhibitors

MAO inhibitors should be used with caution as concomitant administration with beta-blockers may result in bradycardia and an enhanced hypotensive effect. Monitoring of blood pressure and heart rate are recommended during initial use.

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine)

Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”. If a patient is treated with clonidine and metoprolol concurrently and the clonidine treatment is to be discontinued, metoprolol should be stopped several days before the clonidine withdrawal. This is because the hypertension that can follow withdrawal of clonidine, may be increased in patients receiving concurrent beta-blocker treatment.

Paroxetine may increase plasma levels of metoprolol resulting in increased beta-blocking effects.

Nitrates

Nitrates may enhance the hypotensive effect of metoprolol.

Ergotamine

As beta blockers may affect the peripheral circulation, care should be exercised if used together with drugs with similar activity e.g. ergotamine.

Parasympathomimetics

Concurrent use of parasympathomimetics may result prolonged bradycardia.

Sympathomimetics

Metoprolol will antagonize the β_1 effect of sympathomimetic agent but should have little influence on the bronchodilator effects of β_2 agonists at normal therapeutic dose.

General anaesthetics

An increase in the cardio-depressive effect due to the concomitant administration of inhalational anaesthetics is possible; however, since beta blockade can prevent excessive fluctuations in blood pressure whilst the patient is intubated and is rapidly antagonised with beta sympathomimetics, concomitant use is not contraindicated (see section 4.4). Metocor should only be used with great caution in patients who are receiving myocardial depressants such as chloroform, ether or related anaesthetics.

Insulin and oral antidiabetic agents

The blood glucose-reducing effect of insulin and oral blood glucose-reducing drugs can be intensified by beta blockers, in particular non-selective beta blockers. In this case, the dosage of the oral blood glucose-reducing drug must be adjusted.

Alpha blockers such as prazosin, tamsulosin, terazosine, doxazosin

Increased risk of hypotension, especially severe orthostatic hypotension. Caution if metoprolol tartrate is administered together with prazosin for the first time [first dose hypotension].

Skeletal muscle relaxant

Curare muscle relaxant with metoprolol enhanced neuromuscular blockade. Blood pressure should be monitored and dosage adjustment of the antihypertensive be made if necessary.

Lidocaine

Metoprolol can reduce the clearance of lidocaine.

Hepatic enzyme inducers

Plasma levels of metoprolol tartrate may decrease if taken with enzyme inducers [e.g rifampicin].

Mefloquine

Increased risk of bradycardia.

Antacid

An increase in the plasma concentrations of metoprolol has been observed when the drug was coadministered with an antacid.

Alcohol

Alcohol levels in blood may increase and decrease more slowly with concomitant use with metoprolol tartrate.

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive. Care should be taken when combining with other antihypertensive drugs or drugs that might reduce blood pressure, such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefits to improve control of hypertension.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Since there are no well-controlled studies of the use of metoprolol in pregnant women, metoprolol may only be used during pregnancy if the benefits to the mother outweigh the risk to the embryo/foetus. Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long term treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause prolonged delivery and bradycardia in the foetus and the newborn child. There are also reports of hypoglycaemia, hypotension, increased bilirubinaemia and inhibited response to anoxia in newborn children. Therefore the lowest possible dose should be used, and treatment should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 48-72 hours post-partum for signs and symptoms of beta blocking (e.g. cardiac and pulmonary complications).

Beta blockers have not shown potential teratogenic activity in animals, but reduced blood flow in the umbilical cord, growth retardation, reduced ossification and increased numbers of foetal and post-natal deaths.

Breast-feeding:

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother’s plasma. Even though the risk of adverse effects in the breast-feeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity), breast-feeding babies should be monitored for signs of beta blocking (e.g. bradycardia, hypoglycaemia).

4.7 Effects on ability to drive and use machines

As with all beta-blockers, Metocor may affect patient’s ability to drive and operate machinery. It should be taken into account that occasionally dizziness or fatigue may occur. Patients should be warned accordingly. These effects may possibly be enhanced in case of concomitant ingestion of alcohol or after changing to another medicinal product.

4.8 Undesirable effects

Metoprolol is well tolerated, and the undesirable effects are generally mild and reversible. The most commonly reported adverse reaction during treatment is fatigue. Gangrene (in patients with severe peripheral circulatory disorder), thrombocytopenia and agranulocytosis may occur very rarely (less than 1 case per 10,000 patients). The following undesirable effects have been reported during the course of clinical studies or have been reported after routine use.

* In many cases, a link with the use of metoprolol (tartrate) has not been firmly established.

	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)
Blood and lymphatic system disorders					Thrombocyto- penia, Leukopenia
Endocrine disorders				Deterioration of latent diabetes mellitus.	

Metabolism and nutrition disorders			Weight gain.		
Psychiatric disorders			Depression, Concentration problems, Drowsiness or insomnia, Nightmares.	Nervousness, Anxiety.	Forgetfulness or memory impairment, Confusion, Hallucinations, Personality changes (e.g. mood changes).
Nervous system disorders		Dizziness, Headache.	Paraesthesia.		
Eye disorders				Visual disturbances, Dry or irritated eyes, Conjunctivitis.	
Ear and labyrinth disorders					Tinnitus, Hearing problems.
Cardiac disorders		Bradycardia, Balance disturbances (very rarely with associated syncope), Palpitations.	Temporary exacerbation of symptoms of heart failure, First-degree atrioventricular block, Precordial pain.	Functional Heart symptoms, Heart arrhythmia, Conductivity disturbances.	
Vascular disorders	Pronounced blood pressure drop and orthostatic hypotension, very rarely with syncope.	Cold hands and feet.			Necrosis in patients with severe peripheral vascular disorders prior to treatment, exacerbation of claudication intermittens or Raynaud’s syndrome.
Respiratory, thoracic and mediastinal disorders		Functional dyspnoea.	Bronchospasms	Rhinitis	
Gastrointestinal disorders		Nausea, Abdominal pain, Diarrhoea, Constipation	Vomiting	Dryness of mouth	Taste disturbances.
Hepatobiliary disorders				Abnormal LFT values	Hepatitis
Skin and subcutaneous tissue disorders			Rash (psoriasis-like urticaria and dystrophic	Hair loss	Light hypersensitivity reactions, Exacerbation of

			cutaneous lesions), Increased perspiration		psoriasis, new psoriasis manifestation, psoriasis-like dermatological changes
Musculoskeletal and connective tissue disorders			Muscle spasms		Arthritis Arthralgia, Muscle weakness
Reproductive system and breast disorders				Impotence and other sexual dysfunctions, induratio penis plastica (Peyronie’s syndrome).	
General disorders and administration site conditions	Fatigue	Oedema			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Over dosage may lead to pronounced sinus bradycardia, hypotension, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, asystole, QT-prolongation (isolated cases), poor peripheral perfusion, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, respiratory depression, apnoea, fatigue, fine tremor, seizures, sweating, paraesthesia, possible oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia, renal effects, transient symptoms of myasthenia.

In certain cases, especially among children and adolescents, CNS-symptoms and respiratory depression may predominate.

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

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

Management

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

Active charcoal, gastric lavage if necessary. NOTE! Atropine (0.25-0.5 mg i.v. to adults, 10-20 micrograms/kg to children) should be administered prior to gastric lavage (due to the risk of vagal stimulation). Intubation and assisted ventilation should occur based on a very wide indication. Adequate volume substitution. Glucose infusion. ECG monitoring. Atropine sulphate may be administered (0.5 - 2.0 mg intravenously) for blocking the vagus nerve. This can be repeated.

In case of severe hypotension, bradycardia or in risk of heart failure, the patient could be given a beta-1 agonist (e.g. prenalterol or isoprenaline) intravenously at intervals of 2-5 minutes or as continuous infusion until achieving the desired effect. If a selective beta-1 agonist is unavailable, dopamine may be used.

If the desired effect is not achieved, another sympathomimetic agent may be used, e.g. dobutamine or noradrenaline.

The patient may also be given 1-10 mg glucagon. It may be necessary to use a pacemaker. A beta-2 agonist may be administered intravenously to prevent bronchospasms in the patient, the patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

Metoprolol cannot be effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO7AB02

Beta blocking agents, selective

Mechanism of action

Metocor is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta₁ receptors [i.e. those mediating adrenergic stimulation of heart rate and contractility and the release of free fatty acids from fat stores] than on beta₂-receptors, which are chiefly involved in broncho and vasodilation. Metocor therefore possesses the therapeutically desirable effects of shielding the heart and blood vessels from the harmful effects of excessive adrenergic challenge during stress or exercise with minimal interference with respiratory function or vascular tone.

Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect.

Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart.

Metoprolol reduces tachycardia, decreases the cardiac output and the contractility, and lowers the blood pressure.

5.2 Pharmacokinetic properties

Absorption

Metoprolol is completely absorbed after an oral dose, peak plasma concentrations occurring 1.5 – 2 hours after dosing. Due to a pronounced first passage metabolism for metoprolol, the bioavailability of a single oral dose is approx. 50 %.

Concomitant intake of food increases bioavailability to approximately 70%.

Distribution and Biotransformation

Metoprolol is widely distributed; it crosses the blood-brain barrier, the placenta, and is excreted in breast milk. Only a small fraction of metoprolol (approx. 5-10 %) binds to plasma proteins.

Metoprolol is metabolized by hepatic oxidation. The three known main metabolites have been shown not to have a clinically significant beta blocking effect.

Metoprolol is metabolised primarily, but not solely, by the hepatic enzyme cytochrome (CYP) 2D6. Due to the polymorphism of the CYP 2D6 gene, the turnover rates vary with the individual. Individuals with poor metabolic capacity (approx. 7-8 %) exhibit higher plasma concentrations and slower elimination than individuals with good metabolic capacity. The plasma concentrations are stable and repeatable in the individuals, however.

Elimination

More than 95 % of an oral dose is excreted in urine. Approximately 5 % of the dose is excreted in unchanged form; in single cases up to an entire 30 %. The elimination half-life of metoprolol in plasma is 3.5 hours on average (interval 1-9 hours). Total clearance is approx. 1 L/min.

The pharmacokinetics of metoprolol in the elderly is not significantly different from that in younger populations. The systemic bioavailability and elimination of metoprolol is normal in renal failure patients. The elimination of metabolites is slower than normal, however. Significant accumulation of metabolites has been observed in patients with a glomerular filtration rate of less than 5 mL/min. The metabolite accumulation does not potentiate the beta blocking action of metoprolol.

Patients with hepatic cirrhosis may experience an increase in the bioavailability of metoprolol and a decline in total clearance. However, the exposure increase only has clinical relevance in patients with severely impaired hepatic function or portocaval shunt. In patients with portocaval shunt, the total clearance is approx. 0.3 L/min, and the AUC values are approx. six times larger than in healthy individuals.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Microcrystalline Cellulose
Magnesium Stearate
Colloidal Anhydrous Silica
Hypolose
Calcium Hydrogen Phosphate Dihydrate
Crospovidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Metocor 100 mg tablets are blister packed in blisters of polypropylene, welded on an internally film-coated aluminium semi-rigid support and are available in pack sizes of 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/008/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 July 1995

Date of last renewal: 14 July 2010

10 DATE OF REVISION OF THE TEXT

January 2017