Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metocor 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg metoprolol tartrate.
Excipients: Contains lactose monohydrate 49.75 mg.

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 400 mg 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 chlortalidone 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
Metoprolol blood levels are likely to increase substantially in patients with hepatic impairment. Therefore, metoprolol should be initiated at low doses with cautions gradual dose titration according to clinical response.

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:

• Known hypersensitivity to metoprolol and related derivatives, or to any of the excipients listed;
hypersensitivity to other beta-blockers (cross sensitivity between beta-blockers can occur)
• Grade II or III atrioventricular block
• Decompensated heart failure
• Manifest and clinically significant bradycardia (heart frequency < 50/min.)
• Cardiogenic shock
• Sick-sinus syndrome
• Severe peripheral arterial circulatory disorders
• Hypotension
• Severe bronchial asthma or history of severe bronchospasm
• Untreated phaeochromocytoma (see section 4.4)
• Metabolic acidosis
• Higher grade sinoatrial block
• 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

Bronchospastic disease
In general, patients with bronchospastic diseases should not be given beta blockers, including metoprolol. However, due to its relative cardioselectivity, oral metoprolol 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 $beta_1$-selectivity is not absolute, a $beta_2$-agonist should be administered concomitantly, and the lowest possible dose of metoprolol should be used.

Diabetic patients
Metoprolol should be used with caution, especially in those who are receiving insulin or oral hypoglycaemic agents.

Diabetic patients should be warned that beta blockers, including metoprolol, may mask the tachycardia occurring with hypoglycemia. However, other manifestations of hypoglycemia such as dizziness and sweating may not be significantly suppressed, and sweating may be increased.

Cardiovascular system
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.

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

Myocardial infarction
If significant hypotension occurs in patients with myocardial infarction, metoprolol should be discontinued, and the hemodynamic status of the patient and the extent of myocardial ischemia carefully assessed. Intensive hemodynamic monitoring may be required and appropriate treatment modalities should be instituted. If hypotension is associated with significant bradycardia or atrioventricular block, treatment should be directed at reversing these.

In the case of increasing bradycardia (heart rate less than 50 to 55 beats/min), the dosage should be reduced, or treatment gradually discontinued.

Abrupt discontinuation
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.

Peripheral circulatory disorders
Metoprolol 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).

Pheochromocytoma
In patients with known or suspected pheochromocytoma, metoprolol should always be given in combination with an alpha blocker and only after the alpha blocker has been initiated (see section 4.3).

Anaesthesia and surgery
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. If it is thought necessary to stop beta blocker therapy, including metoprolol, before surgery, this should be done gradually and completed approximately 48 hours before general anaesthetic.

Prinzmetal's angina
Beta blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). Relatively selective $beta_1$-receptor blockers, such as metoprolol, can be used in such patients, but only with the utmost care.

Thyrotoxicosis

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.

Psoriasis
Beta blockers may trigger or exacerbate psoriasis.

Oculomucocutaneous syndrome
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.

Anaphylactic reactions
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).

Special populations

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

Geriatric patients
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.

Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests.

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

4.5 Interaction with other medicinal products and other forms of interactions

The following combinations with metoprolol should be avoided:

Calcium channel blockers (IV use)
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 metoprolol because there is a risk of cardiac arrest in this situation (see section 4.4).

The following combinations with metoprolol may require consideration:

Interactions resulting in effects on metoprolol:

Calcium channel blockers (oral use)
Co-administration of a beta-adrenergic antagonist with a calcium channel blocker may produce an additive reduction in myocardial contractility due to negative chronotropic and inotropic effects. Patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol should be closely monitored.

Anti-arrhythmic drugs
Beta blockers may potentiate the negative inotropic effect of anti-arrhythmic agents and their effect on atrial-conduction time. Particularly, in patients with pre-existing sinus node dysfunction.

Co-administration with amiodarone may result in additive electro-physiologic effects including bradycardia, sinus arrest and atrioventricular block.

Anti-arrhythmic agents such as quinidine, tocainide, procainamide, ajmaline, amiodarone, flecainide and disopyramide may potentiate the effects of metoprolol on heart rate and atrioventricular conduction.

Non-steroidal anti-inflammatory drugs (NSAID)
Co-administration of NSAIDs including COX-2 inhibitors with a beta blocker may decrease the antihypertensive effect of metoprolol, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by NSAIDs.

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 fluvoxamine, fluoxetine, paroxetine, sertraline, clomipramine, desipramine or bupropion, antipsychotics such as chlorpromazine, fluphenazine, haloperidol or 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. On commencement of treatment with these medicinal products in patients being treated with metoprolol the dose of metoprolol may need to be reduced.

Digitalis glycosides
Digitalis glycosides in connection with beta-receptor blockers, can increase the atrioventricular conduction time and induce bradycardia. Monitoring heart rate and PR interval is recommended.

Sympathomimetics
Co-administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine and xanthine derivatives (including antitussives or nose and eye drops) with a beta blocker may enhance the pressor response resulting in hypertension due to mutual inhibition of therapeutic effects. However, this is less likely with therapeutic doses of $beta_1$-selective drugs than with non-selective beta blockers.

Other anti-hypertensive drugs
The effect of metoprolol ad other antihypertensive drugs on blood pressure are usually additive.
Patients receiving concurrent treatment with catecholamine depleting drugs and
patients who are concomitantly receiving sympathetic ganglion blockers, or other beta blockers (including in the form of eye drops, such as timolol) or monoamineoxidase (MAO) inhibitors, must continue being monitored. In addition, possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the concomitant administration with an irreversible MAO inhibitor.

Nitroglycerin
Nitroglycerin may enhance the hypotensive effect of metoprolol.

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.

Interactions resulting in effects on other drugs

Anti-adrenergic agents
The antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta blockers. Beta- adrenergic blockers may also potentiate the postural hypotensive effect of the first dose of prazosin, probably by preventing reflex tachycardia. On the contrary, beta-adrenergic blockers may also potentiate the hypertensive response to discontinuation of clonidine in patients receiving concomitant clonidine and beta-adrenergic blockers. If a patient is treated with clonidine and metoprolol concomitantly, and clonidine treatment is to be discontinued, metoprolol should be stopped several days before clonidine is discontinued.
Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

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].

Lidocaine

Metoprolol can reduce the clearance of lidocaine leading to increase lidocaine effects.

Ergot alkaloid
Co-administration with beta blockers may enhance the vasoconstrictive action of ergot alkaloids.

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

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

Hydralazine
Co-administration of hydralazine may inhibit pre-systemic metabolism of metoprolol leading to increased concentrations of metoprolol.

Dipyridamole
In general, administration of a beta blocker should be withheld before dipyridamole testing, with careful monitoring of the heart rate following dipyridamole injection.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
Risk summary
There is a limited amount of data on the use of metoprolol in pregnant women.
Experience with metoprolol in the first trimester of pregnancy is limited, but no fetal malformations attributable to metoprolol have been reported. The risk to the fetus/mother is unknown. However, beta blockers may reduce placental perfusion.
Embryotoxicity and/or fetotoxicity in rats and rabbits were noted starting at doses of 50 mg/kg in rats and 25 mg/kg in rabbits, as demonstrated by increases in preimplantation loss.

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.
The doctor should be immediately informed, if pregnancy is confirmed.

In the case of treatment with metoprolol during pregnancy, the lowest possible dose should be used, and treatment discontinuation should be considered 2 to 3 days before delivery to avoid increased uterine contractility and effects of a beta-blockade in the newborn baby (for example, bradycardia, hypoglycemia).

Fetal/Neonatal adverse reactions
Neonates of women with hypertension who are treated with beta-blockers during late pregnancy may be at increased risk for bradycardia and hypoglycemia.

Lactation:
Risk Summary

Metoprolol is secreted into the breast: with therapeutic doses, an infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of metoprolol. Relative infant dose through breast milk is less than 1.0% of maternal weight-adjusted dose.
Nevertheless, breast-fed infants should be closely observed for signs of beta-blockade.

Females and males of reproductive potential

Infertility:
The effects of metoprolol on human fertility have not been studied.

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.

The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare < 1/10,000

	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					Thrombocytopenia Leukopenia
Endocrine disorders				Deterioration of latent diabetes mellitus	
Metabolism and nutrition disorders			Weight gain		
Psychiatric disorders			Concentration problems Drowsiness or insomnia	Nervousness Anxiety Depression Nightmares	Forgetfulness or memory impairment Confusion Hallucinations Personality changes (e.g. mood changes)
Nervous system disorders		Dizziness Headache		Depressed level of consciousness Somnolence Insomnia Paraesthesia	
Eye disorders				Conjunctivitis	Visual disturbances, (e.g. blurred vision) Dry or irritated eyes
Ear and labyrinth disorders					Tinnitus, Hearing problems e.g. hypoacusis or deafness, in doses exceeding those recommended

Cardiac disorders		Bradycardia Balance disturbances (very rarely with associated syncope)	Temporary exacerbation of symptoms of heart failure First-degree atrioventricular block Precordial pain	Functional heart symptoms Heart arrhythmia Heart failure Palpitations	Conductivity disturbances Chest pain
Vascular disorders		Pronounced blood pressure drop and orthostatic hypotension, very rarely with syncope		Oedema Raynaud's phenomenon	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 (which may occur in patients without a history of obstructive lung disease)		Rhinitis
Gastrointestinal disorders		Nausea Vomiting Abdominal pain		Diarrhoea Constipation	Dryness of mouth Retroperitoneal fibrosis
Hepatobiliary disorders					Hepatitis
Skin and subcutaneous tissue disorders				Rash (psoriasis-like urticaria and dystrophic cutaneous lesions)	Light hypersensitivity reactions Increased perspiration (hyperhidrosis) Hair loss (alopecia) Exacerbation of psoriasis, new psoriasis manifestation, psoriasis-like dermatological changes
Musculoskeletal and connective tissue disorders				Muscle spasms	Arthritis
Reproductive system and breast disorders					Impotence and other sexual dysfunctions, induratio penis plastica (Peyronie's syndrome)
General disorders and administration		Fatigue			

site conditions					
Investigations					Weight increase Liver function test abnormal

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

Signs and symptoms:
Over dosage may lead to pronounced sinus bradycardia, severe hypotension, atrioventricular block, myocardial infarction, 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 20 min 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.

In the event of a potentially life-threatening oral overdose, vomiting and gastric lavage should be induced (if within 4 hours after ingestion of metoprolol) and/or activated charcoal should be used to remove the drug from the gastrointestinal tract.

Metoprolol cannot be effectively removed by haemodialysis.
Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.
The beta blocker withdrawal phenomenon (see section 4.4) may occur after overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO7AB02
Beta blocking agents, cardioselective

Mechanism of action (MAO)
Metoprolol is a cardioselective beta-blocker; it blocks $beta_1$-adrenergic receptors (which are mainly located in the heart) at lower doses than those needed to block $beta_2$-receptors, which are mainly located in the bronchi and peripheral vessels. It has no membrane-stabilizing effect nor partial agonist (intrinsic sympathomimetic) activity.

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 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 normalized 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 in blood pressure with metoprolol appears to parallel this gradual decrease in total peripheral resistance.

In patients with angina pectoris, metoprolol reduces the frequency and severity of ischemic 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 primarily due 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 add-on treatment for 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. Pharmacokinetic and pharmacodynamic studies indicate that 30% of maximum beta-1-adrenoreceptor antagonistic activity is essential for minimum pharmacodynamic effect which is observed with about 45 nmol/L metoprolol in plasma.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of conventional tablets, metoprolol is rapidly and almost completely absorbed from the gastrointestinal tract. The drug is absorbed evenly throughout the gastrointestinal tract. Absorption of metoprolol from metoprolol retarded tablets 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 pre-systemic elimination differs between individuals because of genetic differences in oxidative metabolism. Although the plasma profiles exhibit wide inter-subject variability, they are reproducible within an individual. Following 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%.

Distribution
Metoprolol is extensively and rapidly distributed, with a reported volume of distribution of 3.2 to 5.6 L/kg. The apparent volume of distribution at steady-state (Vss) in extensive metabolizers (4.84 L/kg) is relatively higher than poor metabolizers (2.83 L/kg). 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. In patients with hypertension, metoprolol concentrations in cerebrospinal fluid are similar to those in plasma. Metoprolol is not a significant P-glycoprotein substrates indicating that inter-individual variability in pharmacokinetics of metoprolol can be majorly due to CYP2D6 metabolism.

Biotransformation/Metabolism
Metoprolol is extensively metabolized by enzymes of the cytochrome P450 system in the liver. The main metabolic pathways of metoprolol are alpha-hydroxylation,
O-demethylation, and oxidative deamination. Alpha-hydroxylation of metoprolol is stereo-selective. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6).

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 metabolizers the half-life may be 7 to 9 hours. Following single oral administration of 100 mg metoprolol, the median clearances were 31, 168, and 367 L/h in poor metabolizers, extensive metabolizers, and ultra-rapid metabolizers, respectively. The renal clearance of the stereo-isomers does not exhibit stereo-selectivity in renal excretion. 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 metabolizers, 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.

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

Food effect
Food appeared to increase the rate of absorption of metoprolol leading to a slightly higher maximum plasma concentration at earlier time. However, it does not have a significant impact on the clearance or the time at which the maximum peak concentration is observed (T_{max}).
In order to minimize the effect-variations within the individual, it is recommended that metoprolol should always be taken in standardized relation with food: If the physician asks the patient to take metoprolol either before or with breakfast then the patient should continue taking metoprolol with same dosing schedule during the course of therapy.
Metoprolol retarded formulations can be taken with or without meals, preferably in the morning.

Special populations
Geriatric patients (>65 years of age or older)
The geriatric population may show slightly higher plasma concentrations of metoprolol as a combined result of a decreased metabolism of the drug in elderly population and a decreased hepatic blood flow. However, this increase is not clinically-significant or therapeutically-relevant. Metoprolol does not accumulate on repeated administration and there is no need to adjust the dose in elderly patients.

Patients with renal impairment
Pharmacokinetics of metoprolol is not impacted in patient with renal impairment. However, there is a possibility of accumulation of one of its less active metabolite in patients with a creatinine clearance below 5 mL/min and this accumulation would not influence the beta-blocking properties of metoprolol. Patients with renal impairment may usually be treated with normal doses.

Patients with hepatic impairment
Since the drug is primarily eliminated by hepatic metabolism, hepatic impairment may impact the pharmacokinetics of metoprolol. The elimination half-life of metoprolol is considerably prolonged, depending on severity (up to 7.2 h), in patients with liver impairment.

Patients with a portacaval anastomosis
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.

Patients with inflammatory disease
Inflammatory disease has no effect on the pharmacokinetics of metoprolol.

Patients with hyperthyroidism
Hyperthyroidism may increase the pre-systemic clearance of metoprolol.

Ethnic sensitivity
The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizer phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolizers. CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizer with normal CYP2D6 activity.

Effect of gender
There is no significant evidence to suggest a possible difference in elimination between the male and the female population, gender-specific recommendations for dosing of metoprolol are not necessary.

5.3 Preclinical safety data

Reproductive toxicity
Animal Data
Reproductive toxicity studies in mice, rats and rabbits did not show any teratogenic potential for metoprolol tartrate. Embryotoxicity and/or fetotoxicity in rats and rabbits were noted starting at doses of 50 mg/kg in rats and 25 mg/kg in rabbits, as demonstrated by increases in preimplantation loss, decreases in the number of viable fetuses per dose, and/or decreases in neonatal survival. High doses were associated with some maternal toxicity, and growth delay of the offspring in utero, which was reflected in minimally lower weights at birth.

Metoprolol tartrate has been associated with reversible adverse effects on spermatogenesis starting at oral dose levels of 3.5 mg/kg in rats (0.1 times the maximum human dose based on body surface area). However, no effect on reproductive performance was seen in male rats administered metoprolol tartrate at doses ≥50 mg.kg (approximate to the maximum human dose).
Genotoxicity
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

Lactose Monohydrate
Maize Starch
Microcrystalline Cellulose
Magnesium Stearate
Colloidal Anhydrous Silica
Hyprolose
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
Newtown
Bantry
Co. Cork
Ireland

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

September 2019