SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoprolol Tartrate 50 mg Film-coated Tablets
Metoprolol Tartrate 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg Metoprolol Tartrate Ph. Eur as the active substance.
Excipients of known effect: Lactose monohydrate 14.5 mg per tablet.

Each film-coated tablet contains 100mg Metoprolol Tartrate Ph. Eur as the active substance.
Excipients of known effect: Lactose monohydrate 29.0 mg per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet (Tablet)

Pink, round biconvex film-coated tablets with 'B' & 'L' separated by notch break line on one side and '50' debossed on other side.

The tablet can be divided into equal halves.

White to off-white, round, biconvex film-coated tablets with 'B' & 'L' separated by notch break line on one side and '100' debossed on other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of:

- Hypertension
- Angina pectoris
- Cardiac arrhythmias especially supraventricular tachyarrhythmias.
- Adjunct to treatment of thyrotoxicosis.

- Early intervention with Metoprolol Tartrate in myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics. Metoprolol Tartrate has been shown to reduce mortality when administered to patients with acute myocardial infarction.
- Prophylaxis of migraine.

Metoprolol Tartrate has been shown to reduce mortality when administered to patients with acute myocardial infarction.

4.2 Posology and method of administration

Posology

The following dosage regimes are intended only as a guideline and should always be adjusted to the individual requirements of the patient but should not exceed 400 mg/day.

Adults

Hypertension: Initially a dose of 100mg per day should be prescribed either as single or divided doses. Depending upon the response the dosage may be increased by 100mg per day at weekly intervals to 200mg daily given in single or divided doses. Combination therapy with a diuretic or vasodilator may also be considered to further reduce blood pressure.

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

Angina Pectoris: Usually 50-100mg 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 50-100mg twice daily.

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

Following the treatment of an acute arrhythmia with metoprolol tartrate injection, continuation therapy with metoprolol tablets should be initiated 4-6 hours later. The initial oral dose should not exceed 50mg twice daily.

Myocardial Infarction - Early intervention:

In order to achieve optimal benefits from intravenous metoprolol, suitable patients should present within 12 hours of the onset of chest pain. Therapy should commence with 5mg iv every 2 minutes to a maximum of 15mg total as determined by blood pressure and heart rate. The second or third dose

should not be given if the systolic blood pressure is less than 90mmHg, the heart rate is less than 40 beats/minute and the P-Q time is greater than 0.26 seconds, or if there is any aggravation of dyspnoea or cold sweating. Orally, therapy should commence 15 minutes after the injection with 50mg every 6 hours for 48 hours. Patients who fail to tolerate the full i.v. dose should be given half the suggested oral dose.

Maintenance: The usual maintenance dose is 200mg daily given in divided doses. The treatment should be continued for at least 3 months.

Thyrotoxicosis
50mg four times daily. Dose should be reduced progressively as euthyroid state is achieved.

Prophylaxis of Migraine: 100-200mg daily, given in divided doses (morning and evening).

Elderly
The optimum dose should be individually determined according to clinical response. There is no evidence to suggest that dosage requirements are different in otherwise healthy elderly patients. However, caution is indicated in elderly patients as an excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.
In patients with significant hepatic dysfunction the lower dosage recommendations will be more appropriate.

Paediatric population
The safety and efficacy of Metoprolol in children has not been established. Metoprolol tartrate is not recommended in children.

Hepatic impairment
In patients with significant hepatic dysfunction dosage reduction may be advised.

Renal impairment
Dose adjustment is not warranted in renal impairment.

Method of administration
Metoprolol tartrate tablets should be administered orally and swallowed unchewed.
The tablets should be taken on an empty stomach

4.3 Contraindications

- Hypersensitivity to the active substance, other β-blockers or to any of the excipients listed in section 6.1

- Asthma or history of bronchospasm
- Atrioventricular block of second or third degree
- Uncontrolled heart failure
- Clinically relevant sinus bradycardia (< 45-50 bpm)
- Prinzmetal's angina
- Sick-sinus syndrome (unless a pacemaker is in situ)
- Severe peripheral arterial disease
- Hypotension
- Untreated phaeochromocytoma
- Metabolic acidosis.
- Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock
- Diabetes if associated with frequent episodes of hypoglycaemia
- Chronic obstructive pulmonary disease
- Renal or hepatic failure
- Therapy resistant hypokalaemia and hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia, anuria.
- The concomitant intravenous administration of calcium blockers of the type verapamil and diltiazem other antiarrhythmics (such as disopyramide) is contraindicated (exception: intensive care unit).

4.4 Special warnings and precautions for use

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a betablockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of betablockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardioselective beta-blockers may have less effect on lung function than non selective beta-blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Therapy with a beta2-stimulant may become necessary or current therapy require adjustment.

Therefore, non-selective beta-blockers should not be used for these patients, and beta-1 selective blockers only with the utmost care.

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

Metoprolol Tartrate tablets 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.

When a beta blocker is being taken, a serious, sometimes even life-threatening deterioration in cardiac function can occur, in particular in patients in whom the action of the heart is dependent on the presence of sympathetic system support. This is due less to an excessive beta-blocking effect and more to the fact that patients with marginal heart function tolerate poorly a reduction in sympathetic nervous system activity, even where this reduction is slight. This causes contractility to become weaker and the heart rate to reduce and slows down AV conduction. The consequence of this can be pulmonary oedema, AV block, and shock. Occasionally, an existing AV conduction disturbance can deteriorate, which can lead to AV block.

In patients with a phaeochromocytoma, an alpha blocker should be given concomitantly

Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

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

Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to an increase of blood pressure and bradycardia.

Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50 to 55 beats/min at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced.

Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged-release tablets than when using regular tablet forms for beta1 selective beta blockers and significantly lower than when using non-selective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy.

In case of unstable or insulin-dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels (see Section 4.5).

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure (see section 4.3). The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers (see also section 4.5).

Beta-blockers may unmask myasthenia gravis.

In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.

Important information regarding the ingredients in this medicine

Lactose: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially (sodium-free).

Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

- Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided. In a patient under betablockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.

- It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia). The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia (see Section 4.4).

- Digitalis glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase auriculo-ventricular conduction time.

- As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.

- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculo-ventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension. Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers (see section 4.3).

- Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure.

Beta-blockers used in conjunction with clonidine increase the risk of "rebound hypertension". If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

- The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.

- NSAIDs (especially indometacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

- Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta-blockers (i.e. eye drops) or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

- Class 1 anti-arrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.

- During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.

- The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing betablockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.

- The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers (see also section 4.4).

- Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

- Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolised beta-blockers.

- Metoprolol may impair the elimination of lidocaine.
- Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers.
- Cocaine may inhibit the therapeutic effects of beta-blockers and increase the risk of hypertension, excessive bradycardia, and possibly heart block.
- Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen induced fluid retention may lead to increased blood pressure.
- Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects.
- Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking.
- Concurrent use requires careful monitoring.
- Concurrent use of aldesleukin may result in an enhanced hypotensive effect.
- Concurrent use of alprostadil may result in an enhanced hypotensive effect.
- There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.
- Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.
- Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.
- The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy:

It is recommended that Metoprolol Tartrate should not be administered during pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant. Should therapy with metoprolol be employed, special attention should be paid to the foetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate.

Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks gestation. Although the drug crosses the placental barrier and is present in cord blood no evidence of foetal

abnormalities have been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long-time treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause bradycardia in the foetus and the newborn child, there are also reports of hypoglycaemia and hypotension in newborn children.

Animal experiments have shown neither teratogenic potential nor other adverse events on the embryo and/or foetus relevant to the safety assessment of the product.

Treatment with metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours post partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Breast-feeding:
The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. The risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity) Cases of neonatal hypoglycaemia and bradycardia have been described with beta-blockers with low plasma protein binding. Metoprolol is excreted in human milk. Even though the metoprolol concentration in milk is very low, breast-feeding should be discontinued during treatment with metoprolol. In case of treatment during breastfeeding, infants should be monitored carefully for symptoms of beta blockade.

4.7 Effects on ability to drive and use machines

As with all beta-blockers, metoprolol may affect patients' ability to drive and operate machinery because of dizziness and fatigue. 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

Frequency estimates:
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); not known (cannot be estimated from the available data)

System Organ Class	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)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Thrombocytopenia, agranulocytosis	
Psychiatric disorders				Depression, nightmares, Nervousness, anxiety, impotence	Hallucinations, personality disorder, Amnesia / Memory impairment	
Nervous system disorders		Dizziness, headache		Alertness decreased, somnolence or insomnia, paraesthesia		
Eye disorders					Visual disturbance (e.g. blurred vision, dry eyes and/or eye irritation	
Ear and labyrinth disorders					Tinnitus, and, in doses exceeding those recommended, "hearing disorders (e.g. hypoacusis or deafness)	
Cardiac disorders		Bradycardia		Heart failure, cardiac arrhythmias, palpitation	Cardiac conduction disorders, precordial pain	Increase in existing intermittent claudication
Vascular disorders		Orthostatic hypotension (occasionally with syncope)		Oedema, Raynaud's phenomenon	Gangrene in patients with pre existing severe peripheral circulatory disorders	
Respiratory, thoracic and mediastinal disorders		Exertional dyspnoea		Bronchospasm (which may occur in patients without a history of obstructive lung disease)	Rhinitis	
Gastrointestinal disorders		Nausea and vomiting, abdominal pain		Diarrhoea or constipation	Dry mouth	Retroperitoneal fibrosis*
Hepatobiliary disorders						Hepatitis
Skin and				Skin rash (in	Photosensitivity,	Occurrence of

Subcutaneous tissue disorders				the form of urticaria, psoriasiform and dystrophic skin lesions)	hyperhidrosis, alopecia, worsening of psoriasis	antinuclear antibodies (not associated with SLE)
Musculo-skeletal and connective tissue disorders				Muscle cramps	Arthritis	
Reproductive system and Breast disorders					Disturbances of Libido and potency	Peyronie's disease*
General disorders and administration site conditions		Fatigue			Dysgeusia (Taste disturbances)	
Investigations					Weight increase, liver function test abnormal	

* (relationship to Metoprolol has not been definitely established).

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Post Marketing Experience
The following adverse reactions have been reported during post-approval use of Metoprolol Tartrate: 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Poisoning due to an over dosage of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, convulsions, nausea, vomiting, cyanosis, hypoglycaemia and occasionally hyperkalaemia. The first manifestations of over dosage appear 20 minutes to 2 hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Absorption of any drug material still present in the gastro-intestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required.

Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v. infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or haemoperfusion may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Pharmacotherapeutic group: Beta blocking agents; ATC code: C07AB02

Mechanism of Action
Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on $beta_1$-receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on $beta_2$-receptors which are chiefly involved in broncho and vasodilation.

5.2 Pharmacokinetic properties

Absorption
Metoprolol is readily and completely absorbed from the gastrointestinal tract. Metoprolol is absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to

approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.

Distribution
Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma-metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ml. Metoprolol is widely distributed, it crosses the blood-brain barrier, the placenta. It is slightly bound to plasma protein.

Biotransformation
Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute. It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination
The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk.

Special population

Elderly:
In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients show no significant differences.

Renal impairment
Renal dysfunction has barely any effect on the bioavailability of metoprolol. However, the excretion of metabolites is reduced. In patients with a glomerular filtration rate of less than 5 ml/minute, a significant accumulation of metabolites has been observed. This accumulation of metabolites, however, produces no increase in the beta blockade.

Hepatic impairment
The pharmacokinetics of metoprolol is influenced only minimally by reduced hepatic function. However, in patients with serious hepatic cirrhosis and a portacaval shunt, the bioavailability of metoprolol can increase, and the total clearance can be reduced. Patients with portacaval anastomosis had a total

clearance of approx. 0.3 litres/minute and AUC values that were 6 times higher than those found in healthy persons.

Severe angina pectoris
Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensives is influenced by this characteristic. In exceptional cases, however, very high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment
It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of pre-existing bronchospastic complaints.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Cellulose Microcrystalline
Sodium Starch Glycolate
Silica Colloidal Anhydrous
Croscarmellose sodium
Starch Pregelatinised
Magnesium Stearate
Hypromellose
Talc
Macrogol 400
Titanium Dioxide (E171)
Ferric Oxide Red (E172) – PL 17907/0129

6.2 Incompatibilities
None known

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in original packaging below 25°C

6.5 Nature and contents of container
PVC / Aluminium foil blisters containing 14 tablets. Pack sizes of 28 and 56 tablets.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Herts, HP4 1EG,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0129
PL 17907/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31/12/2012
Renewal of the authorisation: 17/12/2024

10 DATE OF REVISION OF THE TEXT

24/03/2026