SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoprolol Tartrate 100 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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)

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

The tablet can be divided into equal halves.

4.1 Therapeutic indications

- 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.

4.2 Posology and method of administration

Posology

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

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. Over the dosage range most patients may be expected to respond rapidly and satisfactorily. A further reduction in blood pressure may be achieved if Metoprolol Tartrate is used in conjunction with an antihypertensive diuretic or other hypotensive agent.

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: 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.

Hyperthyroidism: 50mg four times daily. The dosage should be progressively reduced as euthyroid state is slowly achieved.

Myocardial Infarction:

Early intervention:

50mg every 6 hours for 48 hours, preferably within 12 hours of the onset of chest pain.

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

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

Elderly

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 excessively pronounced 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 experience in children is limited, therefore Metoprolol tartrate is not recommended in children.

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
- Patients with unstable or acute decompensated heart failure (pulmonary oedema, hypoperfusion or hypotension), in which case intravenous inotropic therapy is indicated.
- Patients who are receiving, continuously or periodically, inotropic β receptor agonist therapy
- Clinically relevant sinus bradycardia (<50 bpm)
- Sick-sinus syndrome
- Severe peripheral arterial disease,

- Cardiogenic shock
- Hypotension
- Untreated phaeochromocytoma
- Metabolic acidosis.
- The concomitant intravenous administration of calcium antagonists Verapamil and Dilitiazem, due to the risk of Hypotension, AV conduction disturbances, or left ventricular insufficiency occurring.

Metoprolol is also contraindicated when myocardial infarction is complicated by significant bradycardia (< 50 beats/ minute), a P-Q interval of >0.24 seconds, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure.

4.4 Special warnings and precautions for use

A warning stating "Do not take this medicine if you have a history of wheezing or asthma" will appear on the label.

Although cardioselective beta-blockers, including Metoprolol Tartrate, may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers these should be avoided in patients with reversible obstructive airway disease unless there are compelling clinical reasons for their use. Therapy with a beta2- stimulant may become necessary or current therapy requires adjustment.
Metoprolol may induce or aggravate bradycardia and symptoms of peripheral arterial circulatory disorders. If the patient develops increasing bradycardia, (heart rate less than 50 to 55 beats/min) Metoprolol Tartrate should be given in lower doses or gradually withdrawn.

In addition, anaphylactic reactions precipitated by other agents may be particularly severe in patients taking ß-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, ß-blockers, including Metoprolol Tartrate, should be avoided for patients who are at increased risk of anaphylaxis. Abrupt cessation of therapy with a beta-blocker should be avoided, especially in patients with ischaemic heart disease. When possible, Metoprolol Tartrate should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. During its withdrawal, the patient should be kept under close surveillance and replacement therapy should be initiated to prevent exacerbation of angina pectoris where required.

Beta-blockers, including Metoprolol Tartrate, should not be used in patients with untreated congestive heart failure (see section 4.3). This condition should first be stabilised. Additional therapy should also be considered for patients with a history of heart failure or patients who are known to have a poor cardiac

reserve, e.g. diuretics and/or digitalisation. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal product 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 the case of increasing bradycardia, the dosage should be reduced, or treatment, gradually discontinued.

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

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

Metoprolol Tartrate should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents (see section 4.5). In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy. Metoprolol Tartrate may mask some of the symptoms of hypoglycaemia by inhibition of sympathetic nerve functions and patients should be warned accordingly

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

In patients with significant hepatic dysfunction (e.g. Liver Cirrhosis) it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver the bioavailability may thus be increased

The administration of adrenaline to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with $beta_1$-selective drugs.

Metoprolol Tartrate therapy should be brought to the attention of the anaesthetist prior to general anaesthesia. The benefits of continuing a

treatment with a beta-blocker, including Metoprolol Tartrate, should be balanced against the risk of withdrawing it in each patient. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation. However, the risk of hypertension may be increased. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. In a patient under beta-blockade, the anaesthetic selected should be one exhibiting as little negative inotropic activity as possible (halothane/nitrous oxide). The patient may be protected against vagal reactions by intravenous administration of atropine.

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

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration.

The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

The full oculomucocutaneous syndrome, as described elsewhere with practolol, has not been reported with Metoprolol Tartrate. However, part of this syndrome (dry eyes either alone or, occasionally, with skin rashes) has occurred. In most cases the symptoms cleared when Metoprolol Tartrate treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of Metoprolol Tartrate should be considered. (see advice about discontinuation above).

This medicinal product contains lactose. 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 effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.

As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity, e.g. ergotamine are given concurrently.

Care should also be exercised when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers (also in the form of eye drops) or MAO inhibitors.

Alpha blockers (prazosine, tamsulosin, terazosine, doxazosine) The acute postural hypotension that can follow the first dose of prazosine may be increased in patients already taking a betablocker.

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

Abrupt withdrawal, particularly if prior to beta blocker discontinuation may increase risk of rebound hypertension.

If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine. This is because the hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Calcium channel blockers

Calcium channel blockers such as verapamil and diltiazem may potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and atrioventricular conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving Metoprolol Tartrate because there is a risk of cardiac arrest in this situation. Patients taking an oral calcium channel blocker of the verapamil type in combination with Metoprolol Tartrate should be closely monitored. In patients with impaired cardiac functions, 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.

CYP2D6 inhibitors

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol (see section 5.2.). Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine =,COX-2 inhibitors, antihistamines, Histamine-2-receptor antagonists and medications for stomach ulcers such as cimetidine.

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.

Class I anti-arrhythmic drugs and amiodarone

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

Paroxetine

May increase plasma levels of metoprolol resulting in increased beta blocking effects

Ergotamine

As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity, e.g. ergotamine are given concurrently

NitratesNitrates may enhance the hypotensive effect of Metoprolol Tartrate.

Narcotics

Narcotics with metoprolol may cause cardiac depression

Digitalis glycosides

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

Sympathomimetics

Metoprolol will antagonise the $beta_1$ effects of sympathomimetic agents but should have little influence on the bronchodilator effects of $beta_2$-agonists at normal therapeutic doses. The administration of adrenaline (epinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with beta1-selective drugs.

ParasympathmimeticsConcurrent use of parasympaythmimetics may result in prolonged bradycardia.**Insulin and oral hypoglycaemic drugs**

In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a $beta_1$-selective drug such as Metoprolol Tartrate than with a non-selective beta-blocker. However, diabetic patients receiving Metoprolol Tartrate should be monitored to ensure that diabetes control is maintained (see section 4.4).

Non-steroidal anti-inflammatory drugs

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

Floctafenine

Beta blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Lignocaine

Metoprolol may impair the elimination of lignocaine.

General anaesthetics

Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers; 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)

Hepatic enzyme inducers/inhibitors

Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine) may increase plasma concentrations.

Prostaglandin synthetase inhibitors

The concomitant use of beta blockers with indomethacin or other prostaglandin synthetase inhibitors can reduce the hypotensive effect of the medicinal product.

Alcohol

During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly.

Skeletal muscle relaxant

Curare muscle relaxant with metoprolol enhanced neuromuscular blockade, whereas baclofen increased the risk of orthostatic hypotension in particular. Monitoring of blood pressure and dosage adjustment of the antihypertensive may be necessary.

Mefloquine

Increased risk of bradycardia

Antacid

An increased plasma concentration of metoprolol was observed when the drug was coadministered with an antacid.

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 Pregnancy and lactation

Pregnancy:

Beta-blockers reduce placental perfusion which may result in intrauterine foetal death, immature and premature deliveries. Metoprolol Tartrate should not be used in pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant.

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. 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.

As a precautionary measure, it is preferable to avoid the use of metoprolol during pregnancy. Nevertheless, metoprolol has been used in pregnancy-associated hypertension under close supervision, after 20 weeks gestation. However, in neonates of treated mothers, beta-blocker pharmacologic effects may persist several days after birth and may induce bradycardia, hypoglycaemia, and respiratory distress. Therefore, if metoprolol is used later in pregnancy, the possible undesirable effects on the fetus and neonate (in particular hypoglycaemia, hypotension, and bradycardia) must be carefully monitored during the first days after birth. The lowest possible dose should be used, and treatment should be discontinued at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of beta-blockade in the newborn baby.

Lactation:

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, breastfeeding should be discontinued during treatment with metoprolol. In case of treatment during breast feeding, 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. This applies to a greater extent at the beginning of treatment. Patients should be warned accordingly

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.

Frequency estimates: very common ($\geq$10%); common ($\geq$1% and < 10%);

uncommon ($\geq$0.1% and < 1%); rare ($\geq$0.01% and < 0.1%); very rare (< 0.01%).

Blood and the lymphatic system disorders	

Very rare	Thrombocytopenia, agranulocytosis
Metabolism and nutrition disorders	
Uncommon	Weight gain
Very rare	Increased VLDL, lower HDL, strengthening of insulin induced hypoglycemia
Psychiatric disorders	
Uncommon	depression, reduced alertness, drowsiness or insomnia, nightmares
Rare	Nervousness, anxiety, impotence, somnolence
Very rare	personality disorder, hallucinations, confusion, Amnesia/ memory impairment.
Nervous system disorders	
Very common	Fatigue
Common	dizziness, headache
Uncommon	Paraesthesia,
Eye disorders	
Rare	visual disturbance (e.g. blurred vision), dry eyes and/or eye irritation, conjunctivitis
Ear and labyrinth disorders	
Very rare	tinnitus, and, in doses exceeding those recommended, hearing disorders (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	Bradycardia, hypertension and postural disorders (very rarely with syncope), palpitations, cold hands and feet
Uncommon	Deterioration of heart failure, cardiogenic shock in patient with acute myocardial infarction*, first degree AV block, edema, and pericardial pain
Rare	heart failure, cardiac arrhythmias, palpitation, conduction disorders
Very rare	, precordial pain,

Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope), Raynaud's phenomenon
Rare	oedema,
Very rare	gangrene in patients with pre-existing severe peripheral circulatory disorders
Respiratory, thoracic and mediastinal disorders	
Common	exertional dyspnoea
Uncommon	bronchospasm (which may occur in patients without a history of obstructive lung disease)
Rare	Rhinitis
Gastrointestinal disorders	
Common	nausea, abdominal pain, diarrhea, constipation
Uncommon	Vomiting
Rare	dry mouth
Not known	retroperitoneal fibrosis (relationship to Metoprolol Tartrate has not been definitely established),
Hepatobiliary Disorders	
Rare	Liver function test abnormalities
Very rare	hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), increased sweating
Rare	Reversible hair loss
Very rare	photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis

Musculoskeletal and connective tissue disorders	
Uncommon	muscle weakness and muscle cramps
Very rare	Arthritis, arthralgia
Reproductive system and breast disorders	
Rare	disturbances of libido and potency
Very rare	Peyronie's disease (relationship to Metoprolol Tartrate has not been definitely established)
General disorders and administration site conditions	
Very rare	Dysgeusia (taste disturbances)
Investigations	

*Excess frequency of 0.4% compared with placebo observed in the COMMIT trial in 46,000 patients with acute myocardial infarction where the frequency of cardiogenic shock was 2.3% in patients who received metoprolol (up to 15 mg intravenous then 200 mg oral) and 1.9% in the placebo group in the subset of patients with low shock risk index. The shock risk index was based on the absolute risk of shock in each individual patient derived from age, sex, time delay, Killip class, blood pressure, heart rate, ECG abnormality, and prior history of hypertension. The patient group with low shock risk index corresponds to the patients in which metoprolol is recommended for use in acute myocardial infarction.

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.

4.9 Overdose

Signs and symptoms

In more severe cases 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 ingestion of Metoprolol Tartrate. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Treatment

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

In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage (if within 4 hours after ingestion of Metoprolol Tartrate) and/or activated charcoal to remove the drug from the gastrointestinal tract, use of plasma or plasma substitutes to treat hypotension and shock. Metoprolol cannot be effectively removed by haemodialysis.

Excessive bradycardia can be countered with atropine 1-2mg intravenously and/or a cardiac pacemaker. . If necessary, this may be followed be a bolus dose of glucagon 10mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/ hour depending on the response. Glucagon has positive inotropic and chronotropic effects on the heart that are independent of beta-adrenergic receptors, and has proved effective in the treatment of resistant hypotension and heart failure associated with beta-blocker overdose; Intravenous beta-agonists administration of prenalterol or isoprenaline should be used to treat bradycardia and hypotension; very high doses may be needed to overcome the beta-blockade. Dopamine, dobutamine or noradrenaline may be given to maintain blood pressure. Dobutamine can be administered at 2.5 to 10 micrograms/kg/minute by intravenous infusion.

Diazepam is the drug of choice for controlling seizures. A β2-agonist or aminophylline can be used to reverse bronchospasm; patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

Administration of calcium ions may also be considered.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Pharmacotherapeutic group: Beta blocking agents; ATC code: C07AB02

Mechanism of Action

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..

Due to these properties, metoprolol is suitable for the treatment of hypertension, angina pectoris, various types of arrhythmia, hyperthyroidism, and moderate to serious congestive heart failure in patients with idiopathic dilated cardiomyopathy and for the prevention of the reoccurrence of infarction and mortality in patients who have had a myocardial infarction and in whom there is a considerable risk of a further infarction or sudden cardiac death.

It has no membrane-stabilising effect or partial agonist (intrinsic sympathomimetic) activity. The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. Catecholamines are released when a person is under physical or mental stress. This means that the usual increase in heart rate, cardiac minute volume, cardiac contractility, and blood pressure caused by an acute increase in levels of catecholamine is reduced by metoprolol. In the presence of high levels of endogenous adrenaline, metoprolol interferes far less with the control of blood pressure than non-selective beta blockers. Metoprolol has less of an effect on the release of insulin and the carbohydrate metabolism than nonselective beta blockers. Metoprolol has much less of an effect on the cardiovascular reaction to hypoglycaemia than non-selective beta blockers. Short-term studies have shown that metoprolol can cause a slight increase in the levels of triglycerides and a reduction in the levels of free fatty acids in the blood. In a few cases, a slight reduction in the HDL (high density lipoprotein) fraction was observed,

although this was less pronounced than in the case of nonselective beta blockers.

5.2 Pharmacokinetic properties

Absorption

Metoprolol is well absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentration increase in a linear manner in relation to dosage. Peak plasma concentrations occur approximately 1.5 - 2 hours after dosing. The bioavailability of a single dose is approximately 50%, increasing to approximately 70% during repeated administration. The bioavailability also increases if metoprolol is given with food.

Distribution

The medicinal product is approx. 5–10% bound to plasma proteins.

Biotransformation

Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolisers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Orientals are PMs.

CYP2D6 poor metabolisers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolisers with normal CYP2D6 activity. None of the metabolites of metoprolol contribute significantly to its beta-blocking effect.

Elimination

Elimination is mainly by hepatic metabolism and the average elimination half-life is 3.5 hours (range 1 to 9 hours). Rates of metabolism vary between individuals, with poor metabolisers (approximately 10%) showing higher plasma concentrations and slower elimination than extensive metabolisers. Within individuals, however, plasma concentrations are stable and reproducible. 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%. Total clearance is approximately 1 litre/ minute.

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Cellulose Microcrystalline

Sodium Starch Glycolate

Silica Colloidal Anhydrous

Crosscarmellose sodium

Starch Pregelatinised

Magnesium Stearate

Hypromellose

Talc

Macrogol 400

Titanium Dioxide (E171)

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 17907/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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04/09/2015