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 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.

5.2 Pharmacokinetic properties

Absorption
Metoprolol is readily and completely absorbed from the gastrointestinal tract.

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
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.

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.

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
- Bradycardia

- Prinxmetal's angina
- Sick-sinus syndrome
- 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 antagonists of the type verapamil and dilitiazem 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.

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 patient develops increasing bradycardia, (heart rate less than 50 to 55 beats/min) Metoprolol Tartrate should be given in lower doses or gradually withdrawn.
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 instable or insulin-dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

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

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.

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

- 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. Betaadrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

- 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 (ie 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 atrialconduction 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 eg 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 (eg rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (eg 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 oestrogeninduced 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:

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. 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).

Lactation:

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. Even though the risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity) breastfeeding babies should be monitored for signs 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 (≥ 10%); common (≥ 1% and < 10%);

uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%); very rare (< 0.01%).

Blood and the lymphatic system disorders	
Very rare	Thrombocytopenia
Psychiatric disorders	

Rare	depression, nightmares
Very rare	personality disorder, hallucinations
Nervous system disorders	
Common	dizziness, headache
Rare	alertness decreased, somnolence or insomnia, paraesthesia
Eye disorders	
Very rare	visual disturbance (e.g. blurred vision), dry eyes and/or eye irritation
Ear and labyrinth disorders	
Very rare	tinnitus, and, in doses exceeding those recommended, hearing disorders (e.g. hypoacusis or deafness)
Cardiac disorders	
Common	Bradycardia
Rare	heart failure, cardiac arrhythmias, palpitation
Very rare	cardiac conduction disorders, precordial pain,
Not Known	increase in existing intermittent claudication
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope)
Rare	oedema, Raynaud's phenomenon
Very rare	gangrene in patients with pre-existing severe peripheral circulatory disorders
Respiratory, thoracic and mediastinal disorders	
Common	exertional dyspnoea
Uncommon	bronchospasm (which may occur in patients without a history of obstructive lung disease)
Very rare	Rhinitis
Gastrointestinal disorders	
Common	Nausea and vomiting, abdominal pain

Rare	diarrhoea or constipation
Not known	retroperitoneal fibrosis (relationship to Metoprolol Tartrate has not been definitely established), Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.
Very rare	dry mouth
Hepatobiliary Disorders	
Not Known	hepatitis
Skin and subcutaneous tissue disorders	
Rare	skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis
Not Known	occurrence of antinuclear antibodies (not associated with SLE)
Musculoskeletal and connective tissue disorders	
Uncommon	muscle cramps
Not Known	Arthritis
Reproductive system and breast disorders	
Very rare	disturbances of libido and potency
Not Known	Peyronie's disease (relationship to Metoprolol Tartrate has not been definitely established)
General disorders and administration site conditions	
Common	fatigue
Investigations	
Very rare	weight increase, liver function test abnormal

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of 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

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 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. 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 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

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

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

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31/12/2012

10 DATE OF REVISION OF THE TEXT

28/11/2017