SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoprolol Tartrate 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg metoprolol tartrate.

Excipients with known effect: Each tablet contains 14.00 mg lactose monohydrate and 0.07 - 0.105 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off white lentil shaped tablets.with a diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension.
- Angina pectoris.
- Cardiac arrhythmias, especially supraventricular tachyarrhythmias.
- Adjunct to treatment of thyrotoxicosis.
- Early intervention with metoprolol in myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics. Metoprolol 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 400 mg/day. The following are guidelines:

Adults

Hypertension: initially a dose of 100 mg per day should be prescribed either as single or divided doses. Depending upon the response the dosage may be increased by 100 mg per day at weekly intervals to 200 mg 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 is used in conjunction with an antihypertensive diuretic or other hypotensive agent.

Metoprolol 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 added into the regime with adjustment of the previous therapy if necessary.

Angina pectoris: 50-100 mg twice or three times daily
In general a significant improvement in exercise tolerance and reduction of anginal attacks may be expected with a dose of 50-100 mg twice daily.

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

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

Myocardial infarction:
Early intervention: 50 mg every 6 hours for 48 hours, preferably within 12 hours of the onset of chest pain.
Maintenance: the usual maintenance dose is 200 mg daily given in divided doses. The treatment should be continued for at least 3 months.

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

Termination of treatment: The dose should be withdrawn gradually over a period of 10 days, the doses diminishing to 25 mg for the last 6 days (see section 4.4).

Special populations

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.

Hepatic impairment
In patients with significant hepatic dysfunction the lower dosage should be considered (see section 5.2).

Renal impairment
No dosage adjustment is usually needed in patients with renal insufficiency (see section 5.2).

Poor metabolisers
Poor metabolisers may require lower than normal doses (see section 5.2).

Children
Not recommended.

Method of administration
Metoprolol tablets should be administered with a drink of water.

4.3 Contraindications

- Hypersensitivity to the active substances, to related derivatives or to any of the excipients listed in section 6.1.
- Severe asthma or history of severe bronchospasm.
- Atrioventricular block of second or third degree.
- Uncontrolled heart failure.
- Clinically relevant sinus bradycardia.
- Sick-sinus syndrome.
- Severe peripheral arterial disease.
- Cardiogenic shock.
- Hypotension.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Metoprolol is also contraindicated when myocardial infarction is complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100 mmHg) 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, 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 $beta_2$- stimulant may become necessary or current therapy require adjustment.

Metoprolol may 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 should be given in lower doses or gradually withdrawn.

In addition, anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers, including metoprolol, 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 should be withdrawn gradually over a period of 10 days, the doses diminishing to 25 mg for the last 6 days. During its withdrawal, the patient should be kept under close surveillance and replacement therapy should be initiated where required.

Beta-blockers, including metoprolol, 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.

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

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.

Metoprolol 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 may mask some of the symptoms of hypoglycaemia by inhibition of sympathetic nerve functions and patients should be warned accordingly.
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 a treated 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.

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 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, 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 β_1-receptor blockers, such as metoprolol, 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 full oculomucocutaneous syndrome, as described elsewhere with practolol, has not been reported with metoprolol. However, part of this syndrome (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 (see advice about discontinuation above).

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet; that is to say essentially "sodium-free".

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.

Prazosin
The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker.

Clonidine
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 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 should be closely monitored.

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 and medications for stomach ulcers such as cimetidine.

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.

Nitroglycerin
Nitroglycerin may enhance the hypotensive effect of metoprolol.

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.

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 beta1-selective drug such as metoprolol than with a non- selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained (see also section 4.4).

The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia (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.

Lignocaine
Metoprolol may impair the elimination of lignocaine.

General anaesthetics
Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers (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.

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

4.6 Fertility, pregnancy and lactation

Metoprolol should not be used in pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant.

If metoprolol is used during pregnancy and lactation special attention should be paid to the foetus, neonate and breast-fed infant for undesirable effects of the drug's beta-blocking action (e.g. bradycardia, hypoglycaemia). 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.

Pregnancy

Beta-blockers reduce placental perfusion which may result in intrauterine foetal death, immature and premature deliveries.

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.

Breast-feeding

The amount of metoprolol ingested via breast milk seems to be negligible with regard to its beta-blocking effects if the mother is treated in doses within the therapeutic range.

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. Patients should be warned accordingly.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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 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 (eg. blurred vision), dry eyes and/or eye irritation
Ear and labyrinth disorders	

Very rare	tinnitus, and, in doses exceeding those recommended, hearing disorders (eg. hypoacusis or deafness)
Cardiac disorders	
Common	Bradycardia
Rare	heart failure, cardiac arrhythmias, palpitation
Very rare	cardiac conduction disorders, precordial pain,
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
Rare	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
Very rare	dry mouth
Not known	retroperitoneal fibrosis (relationship to metoprolol has not been definitely established)
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue	
Rare	skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis
Musculoskeletal and connective tissue disorders	
Rare	muscle cramps
Very rare	Arthritis
Reproductive system and breast	
Very rare	disturbances of libido and potency
Not known	Peyronie's disease (relationship to metoprolol 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: 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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In more severe cases an overdosage 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 overdosage appear 20 minutes to 2 hours after ingestion of metoprolol. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Management

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

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

Atropine may be given intravenously to control significant bradycardia. Intravenous betaagonists such as 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. 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.

Diazepam is the drug of choice for controlling seizures. A β_2-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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07AB02

Metoprolol is a cardioselective beta-adrenergic blocking agent.

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. It has no membrane-stabilising effect nor partial agonist (intrinsic sympathomimetic) activity.

The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility and cardiac output.

5.2 Pharmacokinetic properties

Absorption

Metoprolol is well absorbed after oral administration, peak plasma concentrations occurring 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 and biotransformation

Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk (see section 4.6).

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.

Special populations

Because of variation in rates of metabolism, the dose of metoprolol should always be adjusted to the individual requirements of the patient. As the therapeutic response, adverse effects and relative cardioselectivity are related to plasma concentration, poor metabolisers may require lower than normal doses. Dosage adjustment is not routinely required in the elderly or in patients with renal failure, but dosage may need to be reduced in patients with significant hepatic dysfunction when metoprolol elimination may be impaired.

5.3 Preclinical safety data

There are no further data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Maize starch
Lactose monohydrate
Silica, colloidal anhydrous

Sodium starch
glycolate
Calcium stearate
Silica, hydrophobic colloidal
Povidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Alu transparent blister or PVC/PVDC/Alu blister.
Pack sizes: 28 and 56 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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Lane, London
EC4A 1JP,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/0887

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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28/07/2026