1. NAME OF THE MEDICINAL PRODUCT

Metoprolol Tartrate 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg metoprolol tartrate.

Excipient with known effect:
Each tablet contains 39 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, biconvex tablets marked “ML” score line “50”one side and “G” on reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoprolol is a beta-adrenoreceptor blocking drug indicated for: hypertension, angina pectoris, cardiac arrhythmias especially supraventricular tachyarrhythmias, migraine prophylaxis, adjunct to treatment of hyperthyroidism, long-term prophylaxis after recovery from acute myocardial infarction.

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.

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, 100 mg daily, increased by 100 mg daily at weekly intervals to 200 mg daily if needed, in single or divided (twice daily) 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 tablets are used in conjunction with an antihypertensive diuretic or other hypotensive agent.

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

Angina Pectoris: 50-100 mg two 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: 50 mg two or three times daily is usually sufficient. If necessary the dose can be increased up to 300 mg daily in divided doses.

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

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

Myocardial Infarction:
Early intervention: 50 mg every six hours for 48 hours, commencing 15 minutes after the last intravenous dose of metoprolol, and preferably within 12 hours of the onset of chest pain.

Maintenance: 100 mg twice daily as a maintenance dose. The treatment should be continued for at least 3 months.
Patients who do not tolerate the full intravenous dose of metoprolol should be given half the suggested oral dose.

Paediatric population: Not recommended.

Older people: 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 older patients. However, caution is indicated in older 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.

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

Method of administration

Metoprolol tablets should be administered orally and swallowed unchewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or other beta-blockers, in patients with severe asthma or history of severe bronchospasm, in patients with atrioventricular block of second or third degree, in patients with cardiogenic shock, uncontrolled heart failure, sick sinus syndrome (unless a pacemaker is in situ), hypotension, untreated phaeochromocytoma, severe peripheral circulatory disturbances, clinically relevant sinus bradycardia (<45-50 bpm), after prolonged fasting, and in metabolic acidosis (e.g. in some diabetics).

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

Sudden withdrawal of beta-adrenoceptor blocking drugs should be avoided, especially in patients with ischaemic heart disease as it may result in anginal attacks of increased frequency or severity. Therefore, withdrawal of metoprolol should be gradual over 10 days, reducing the dose to 25 mg daily

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 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, can be used in such patients, but only with the utmost care.

Particular care is required with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure, although they may be used when cardiac failure has been controlled. Digitalisation and/or diuretic therapy should be considered in patients with a history of heart failure. Cardiac failure due to thyrotoxicosis may respond to metoprolol alone, but if other adverse factors are also present it is important to control signs of failure with cardiac glycosides and diuretics.

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).

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

A reduction in heart rate is a pharmacological effect of metoprolol. In rare cases where symptoms may be attributable to the slow heart rate (less than 50 to 55 beats/min), the dose should be reduced or gradually withdrawn.

Metoprolol modifies the tachycardia of hypoglycaemia by inhibition of sympathetic nerve functions and it may prolong the hypoglycaemic response to insulin. Patients should be warned accordingly. Care should be exercised during concomitant use of metoprolol and hypoglycaemic therapy in patients with diabetes mellitus. In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy.

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).

Beta-blockers should be used with great caution in patients with peripheral circulatory disorders (Raynaud's disease/syndrome, intermittent claudication), and bradycardia, as they may aggravate such disorders.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions which 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.

While cardioselective beta-blockers such as metoprolol may have less effect on pulmonary function than non-selective ones, they should be avoided in patients with reversible obstructive airways disease, a history of asthma and/or bronchospasm unless absolutely necessary. When administration of metoprolol is required, the use of a $beta_2$-bronchodilator such as terbutaline may be advisable or current therapy may require adjustment in some cases. When beta-blockers are used in patients with a history of bronchial asthma, the possibility of bronchospasm must be considered.

The label will state "Do not take this medicine if you have a history of wheezing or asthma".

Care is required when transferring patients from clonidine to a beta-adrenoceptor blocking drug. If the two drugs are given concurrently, clonidine should not be discontinued until several days after the withdrawal of the beta-adrenoceptor blocking drug. Because of negative inotropic effects, care is required when prescribing a beta-adrenoceptor blocking drug with Class I antidysrhythmic agents such as disopyramide.Beta-adrenoceptor blocking drugs should be used with caution in combination

with verapamil where ventricular function is impaired. The combination should not be given to patients with conduction abnormalities, nor should either drug be administered intravenously within 48 hours of discontinuing the other.

Care is required during parenteral administration of preparations containing adrenaline to patients receiving beta-adrenoceptor blocking drugs, as in rare instances vasoconstriction, hypertension and bradycardia may occur (see section 4.5).

Care is required when administering anaesthetic agents to patients receiving metoprolol. The anaesthetist should always be informed of the use of a beta-adrenoceptor blocking drug. The risks and benefits of continued beta-blocking therapy in the peri-operative period should be carefully evaluated. If a beta-blocker is withdrawn prior to surgery it 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.

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

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver.

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.

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).

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

Other antihypertensive agents will potentiate the hypotensive action of metoprolol 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.

Parenteral administration of preparations containing adrenaline to patients taking beta-adrenoceptor blocking drugs may, in rare cases, result in vasoconstriction, hypertension and bradycardia. Metoprolol however, has been shown to have minimal effects on presser response to adrenaline even at doses of 200-300 mg daily.

Caution should be exercised when co-administering beta-blockers with similar drugs or other beta-blockers (e.g. eye drops), sympathetic ganglion blocking drugs and MAO inhibitors.

Clonidine
Beta-adrenoceptor blocking drugs can exacerbate the rebound hypertension associated with sudden withdrawal of clonidine. If combination treatment with clonidine is to be discontinued metoprolol should be withdrawn several days before clonidine.

Insulin and oral hypoglycaemic drugs
In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia and mask the warning signs of hypoglycaemia such as tremor and tachycardia. 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 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).

Oral contraceptives appear to increase plasma concentrations of Metoprolol.

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

Lidocaine
Metoprolol may impair the elimination of lidocaine.

Non-steroidal anti-inflammatory drugs
Concurrent treatment with non-steroidal anti-inflammatory drugs such as indometacin may reduce the antihypertensive effect of beta-blockers.

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.

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.

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.

Glyceryl trinitrate
Glyceryl trinitrate may enhance the hypotensive effect of metoprolol.

Digitalis glycosides
Digitalis glycosides, in association with beta-adrenoceptor blocking drugs, may result in excessive bradycardia and/or increase in atrio-ventricular 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.

General anaesthetics
Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers (see section 4.4).

Alcohol
Alcohol potentiates the action of metoprolol. 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

The safety of metoprolol in pregnancy has not been established and its use should be avoided unless the potential benefits are likely to outweigh the possible risks to the foetus.

Beta-adrenoceptor blocking drugs reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries.Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks gestation. Although metoprolol crosses the placental barrier and appears 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.

Metoprolol is excreted in breast milk but the amount is too small to be expected to affect the infant if the mother is treated in doses within the therapeutic range. Breast-fed infants should be monitored if the mother is receiving a beta-blocker. However, breast-feeding is not recommended.

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.

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 (symptoms such as dizziness and fatigue have occasionally been reported in association with the use of beta blockers). Patients should be warned accordingly.

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).

Blood and lymphatic system disorders	
Very rare	thrombocytopenia
Psychiatric disorders	
Rare	depression, decreased mental alertness, somnolence or insomnia, nightmares
Very rare	personality disorder, hallucinations
Nervous system disorders	
Common	dizziness, headache
Rare	paraesthesia
Eye disorders	
Very rare	disturbances of vision (e.g. blurred vision), dry and/or irritated eyes
Not known	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
Rare	heart failure, cardiac arrhythmias, palpitation
Very rare	disturbances of cardiac conduction, precordial pain
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope)
Rare	oedema, Raynaud's phenomenon
Not known	hypotension
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	dryness of the mouth
Not known	retroperitoneal fibrosis (relationship to metoprolol has not definitely been established)
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, increased sweating, loss of hair, worsening of psoriasis
Musculoskeletal and connective tissue disorders	
Rare	muscle cramps
Very rare	arthritis
Reproductive system and breast disorders	
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 gain, liver function test abnormalities
Not known	positive anti-nuclear antibodies

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 at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Signs and symptoms

Clinical features of overdosage may include sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, severe hypotension, bronchospasm, hypoglycaemia, coma, nausea, vomiting, cyanosis, occasionally hyperkalaemia, delirium, convulsions and unconsciousness.
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.

Treatment

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.

Following recent overdosage (if within 4 hours after ingestion of metoprolol), the stomach should be emptied by gastric aspiration and lavage and/or activated charcoal to remove the drug from the

gastrointestinal tract. Severe bradycardia may respond to atropine 1 to 2 mg intravenously. Dopamine, dobutamine or noradrenaline may be given to maintain blood pressure. If necessary, this may be followed by a bolus dose of glucagon 5 to 10 mg intravenously, followed if necessary by an intravenous infusion of glucagon 1 to 5 mg per hour or more according to 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.

If there is no response to glucagon, or if glucagon is unavailable, a beta-adrenoceptor stimulant such as isoprenaline 25 micrograms initially or orciprenaline 0.5 mg or prenalterol may be administered by slow intravenous injection. Occasionally a temporary pacing wire may be required. Metoprolol is not dialysable.

Diazepam is the drug of choice for controlling seizures. A $beta_2$-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 beta-adrenoreceptor blocking agent which has preferential effect on the $beta_1$-receptors chiefly located in the heart (cardioselective). This selectivity diminishes with increased dosage. Metoprolol possesses no intrinsic sympathomimetic activity and membrane stabilising activity is detectable only at doses much greater than those required for beta-blockade. By blocking beta-receptor sites, Metoprolol decreases heart rate and cardiac output, decreases systolic blood pressure upon exercise and reduces reflex orthostatic tachycardia.

5.2 Pharmacokinetic properties

Absorption
Metoprolol is well absorbed after oral administration though first-pass metabolism in the liver results in a significant decrease in bioavailability. Peak plasma concentrations are seen 1.5-2 hours after dosing and the plasma half-life is 3-7 hours. 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
Metoprolol exhibits low (10%) plasma protein binding. Metoprolol crosses the placenta, and is found in breast milk (see section 4.6). It is extensively metabolised by enzymes of the cytochrome P450 system in the liver. Due to genetic polymorphism, rates of metabolism vary between individuals, with poor metabolisers (approximately 7% of Caucasians and less than 1% Orientals are poor metanolisers) showing higher blood levels and slower rates of elimination than extensive metabolisers. None of the metabolites of metoprolol contribute significantly to its beta-blocking effect.

Elimination
Only 3-10% of a metoprolol dose is eliminated unchanged in the kidneys. 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.

Characteristics in Patients

Due to 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 older people 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 preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Povidone K29/32
Silica, colloidal anhydrous
Magnesium stearate
Sodium starch glycollate

6.2. Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25ºC.

Store in the original package in order to protect from light and moisture.

6.5. Nature and Contents of Container

Polypropylene pots with white polyethylene caps and optional polyethylene ullage filler in packs of 28, 30, 56, 60, 84, 90,100, 112, 120, 168, 180 and 500 tablets.

PVdC/foil blister strips in packs of 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180 and 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Viatris
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0143

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th April 1987
Date of latest renewal: 13th May 2003

10 DATE OF REVISION OF THE TEXT

15/05/2026