Public Assessment Report

Decentralised Procedure

Metoprolol Tartrate 50 mg tablets
Metoprolol Tartrate 100 mg tablets

UK/H/4414/001-2/DC
UK licence numbers: PL 30139/0017-18

Intas Pharmaceuticals Limited
LAY SUMMARY

On 23\textsuperscript{rd} September 2011, the MHRA granted Intas Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Metoprolol Tartrate 50 mg and 100 mg tablets (PL 30139/0017 and 0018). These are prescription-only medicines (POM).

The active ingredient, metoprolol tartrate, belongs to a group of drugs called beta blockers. Metoprolol tartrate has an effect on how the heart works and reduces blood pressure. It can be used to treat a number of conditions and can be prescribed to patients:

- to reduce high blood pressure
- with chest pain due to angina
- with fast or irregular heart rhythm
- who have had a heart attack, as protection against a possible further heart attack
- to prevent migraines

Metoprolol Tartrate 50 mg and 100 mg tablets were considered to be generic versions of the UK reference products Betaloc Tablets 50mg and 100mg (PL 17901/0109 and 0108, AstraZeneca UK Ltd) based on the data submitted by Intas Pharmaceuticals Limited.

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Metoprolol Tartrate 50 mg and 100 mg tablets outweigh the risk; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Initial Procedure

| Product Name            | Metoprolol Tartrate 50 mg tablets  
<table>
<thead>
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<th></th>
<th>Metoprolol Tartrate 100 mg tablets</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Metoprolol tartrate</td>
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<tr>
<td>Form</td>
<td>Tablets</td>
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<td>Strength</td>
<td>50 mg, 100 mg</td>
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<td>Intas Pharmaceuticals Limited</td>
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<tr>
<td></td>
<td>Sage House, 319, Pinner Road</td>
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<tr>
<td></td>
<td>North Harrow</td>
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<tr>
<td></td>
<td>Middlesex HA 1 4 HF</td>
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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Metoprolol Tartrate 50 mg and 100 mg tablets (PL 30139/0017 and 0018) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Metoprolol Tartrate 50 mg tablets
Metoprolol Tartrate 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Metoprolol tartrate 50/100 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
50 mg: White to off-white, approximately 8 mm round, biconvex tablet marked on one side and a scoreline on the other side.
100 mg: White to off-white, approximately 10 mm round, biconvex tablet marked on one side and a scoreline on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Hypertension
• Angina pectoris
• Tachyarrhythmias, in particular supraventricular tachycardia
• Maintenance treatment after a myocardial infarction
• Prophylaxis of migraine
Metoprolol is indicated in adults.

4.2 Posology and method of administration
Metoprolol tartrate tablets should be administered orally.
The tablets should be taken on an empty stomach.
The dose must always be adjusted to the individual requirements of the patient. The following are guidelines:

Posology
Hypertension
The usual dose is 100mg to 200mg daily, given as a single dose in the morning, or in divided doses (morning and evening). Begin with 50mg twice daily or 100mg once daily. Dose increments should be at weekly intervals thereafter according to individual patient responses. Maximum dose, usually 200mg daily. If necessary, it may be taken in combination with other antihypertensive drugs.

Angina pectoris
The usual dose is 100 to 200 mg daily, given in divided doses (morning and evening). Begin with 50mg twice daily. Dose increments should be at weekly intervals thereafter according to individual patient responses. Maximum dose, usually 200mg daily (in divided doses). If necessary, it may be taken in combination with other antianginal drugs.
Cardiac arrhythmias
The usual dose is 100 to 150 mg per day, in divided doses (in the morning and in the evening). This dosage may be increased, where necessary.

Myocardial infarctions
Maintenance therapy
The oral treatment can be initiated once the patient is haemodynamically stable. The maintenance dose is 100 mg of metoprolol tartrate twice a day (in the morning and in the evening).

Prophylaxis of migraine
The usual dose is 100 to 200 mg per day, in divided doses, in the morning and evening.

Impaired renal function
The dosage does not need to be adjusted in patients with reduced renal function.

Impaired hepatic function
Usually a dose adjustment in patients suffering from liver cirrhosis is not necessary because Metoprolol has a low protein binding (5-10%). However, in patients with severe hepatic dysfunction a reduction in dosage may be necessary.

Elderly patients
No dosage adjustment is required in otherwise healthy elderly patients. However, caution is advised in elderly patients as a fall in blood pressure or excessive bradycardia may have more pronounced effects.

Children
The experience in children is limited, therefore Metoprolol tartrate is not recommended in children.

4.3 Contraindications

- Hypersensitivity to the active ingredient, other β-blockers or to any of the excipients.
- Second-or third-degree AV block
- 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
- Severe bradycardia (<50 bpm)
- Sick sinus syndrome
- Cardiogenic shock
- Severe peripheral arterial disease
- Asthma or a history of bronchospasm
- Untreated phaeochromocytoma
- Metabolic acidosis
- The concomitant intravenous administration of calcium antagonists of verapamil and Diltiazem, due to the risk of hypotension, AV conduction disturbances, or left ventricular insufficiency occurring
- Hypotension

Metoprolol is not indicated for patients with myocardial infarction and a heart rate of <50 beats/minutes, a P-Q interval of >0.24 seconds, or systolic blood pressure of <100 mg Hg and/or severe congestive heart failure.

4.4 Special warnings and precautions for use

A sudden discontinuation of beta blockade can be hazardous and should therefore be avoided. If treatment with Metoprolol tartrate needs to be discontinued, then this should be effected, as a rule, over at least 2 weeks, by halving the dosage incrementally until the patient is taking 25 mg of metoprolol per dose (half a 50 mg tablet). This lowest dosage should be taken for at least 4 days until treatment is discontinued completely. Throughout this period, above all patients with ischaemic heart disease should be carefully monitored, since the risk of coronary events, including sudden cardiac death, is elevated whilst beta blockade is being discontinued. Hypertension and arrhythmia can also occur.

Even though metoprolol, at the usual dosages, has less of a negative impact on the bronchial musculature than non-selective beta blockers, care should still be taken. In patients with bronchial
asthma who are being treated with Metoprolol, bronchodilators that selectively stimulate β₂ receptors, e.g. terbutaline, may be prescribed concomitantly if necessary. If the patient is already taking a β₂ receptor stimulator, it may sometimes be necessary to adjust the dosage thereof.

Since beta blockers can affect the glucose metabolism, vigilance is advisable in patients with diabetes mellitus. The impact on the glucose metabolism and the masking effect on the symptoms of hypoglycaemia are less pronounced in patients treated with metoprolol than in those treated with non-selective beta blockers (in particular tachycardia).

Metoprolol Tartrate tablets may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.

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

In the case of increasing bradycardia, the dosage should be reduced, or treatment, gradually discontinued.

Although contra-indicated in severe peripheral arterial circulatory disturbances (see Section 4.3), in the case of peripheral circulatory disorders, such as Raynaud’s disease or peripheral arterial disease, the clinical picture may deteriorate, principally due to the medicinal product’s hypotensive effect. Beta blockers should be administered with great caution if a deterioration in the clinical picture occurs.

If Metoprolol tartrate is prescribed to a patient with a phaeochromocytoma, an alpha blocker also needs to be administered.

Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. In patients who have to undergo an operation, it is not recommended that beta blocker treatment be discontinued. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

In patients who are taking a beta blocker, the occurrence of an anaphylactic shock is more serious.

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 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 β₁-selective drugs

Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). However, relatively selective β₁-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.

In the presence of liver cirrhosis the bioavailability of metoprolol may be increased.

In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy.

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with beta-blockers.
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.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Medicinal products that have an enzyme-inducing and enzyme-inhibiting effect can have an impact on the plasma level of metoprolol. Metoprolol plasma levels increase in the case of the concomitant use of medicinal products that are metabolised by CYP2D6, such as anti-arrhythmic drugs, antihistamines, histamine-2-receptor antagonists, antidepressants, antipsychotics, and COX-2 inhibitors. Rifampicin reduces the plasma level concentration of metoprolol. Alcohol and hydralazine increase the plasma level of metoprolol.

**Calcium antagonists** In the case of the concomitant use of calcium antagonists of the verapamil or diltiazem types, an increase in negative inotropic and chronotropic effects can occur. Calcium antagonists of the verapamil type should not be administered intravenously to patients who are being treated with beta blockers, due to the risk of hypotension, AV conduction disturbances, and left ventricular insufficiency (see section 4.3). In patients with impaired cardiac function, 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.

**Sympathetic ganglion blockers, or other beta blockers** Patients who are concomitantly receiving sympathetic ganglion blockers, or other beta blockers (including in the form of eye drops) must continue being monitored.

**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.

**Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine)** Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

The concomitant use of clonidine with a non-selective beta blocker, and possibly also with a selective beta blocker, increases the risk of rebound hypertension. If clonidine is administered concomitantly, the administration of the clonidine medication needs to be continued for some time after therapy is discontinued.

**Anti-arrhythmic drugs** Caution is advisable in the case of the concomitant use of some anti-arrhythmic drugs, such as those of the quinidine or amiodarone types, and propafenone since beta blockers can intensify the negative inotropic and negative dromotropic effects thereof.

**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

**Nitrates** Nitrates may enhance the hypotensive effect of metoprolol

**Narcotics** Narcotics with metoprolol may cause cardiac depression.

**Digitalis Glycoside** Concurrent use of digitalis glycoside may result in excessive bradycardia and/or increase in atrioventricular conduction time

**Parasympathomimetics** Concurrent use of Parasympathomimetics may result prolonged bradycardia.

**Sympathomimetics** Metoprolol will antagonize the β1 effect of sympathomimetic agent but should have little influence on the bronchodilator effects of β2 agonists at normal therapeutic dose. 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.
Inhalational anaesthetics  An increase in the cardio-depressive effect due to the concomitant administration of inhalational anaesthetics is possible; 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).

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.

Insulin and oral antidiabetic agents The blood sugar-reducing effect of insulin and oral blood sugar-reducing drugs can be intensified by beta blockers, in particular non-selective beta blockers. In this case, the dosage of the oral blood sugar-reducing drug must be adjusted.

Alpha blockers such as prazosine, tamsulosin, terazosine, doxazosine Increased risk of hypotension, especially severe orthostatic hypotension.

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

Skeletal muscle relaxant Curare muscle relaxant with metoprolol enhanced neuromuscular blockade. Whereas baclofen increased risk of orthostatic hypotension in particular. Monitoring of blood pressure and dosage adjustment of the antihypertensive if necessary.

Lidocaine Metoprolol can reduce the clearance of lidocaine.

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.

Mefloquine Increased risk of bradycardia

Antacid showed an increase in the plasma concentrations of metoprolol 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 Fertility, Pregnancy and lactation

Pregnancy
Animal studies have not shown teratogenic effect at clinically relevant concentrations.

Beta blockers reduce placental perfusion, which may result in intrauterine fetal death, immature and premature deliveries but to date prospective studies have not reported an increased risk of congenital defects in humans. Metoprolol crosses the placenta and is present in cord blood, but no evidence of fetal abnormalities has been reported.

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.

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, breast-feeding 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 has influence on the ability to drive and use machines because of dizziness and fatigue. This applies to a greater extent at the beginning of treatment. Patient 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 reactions 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.

The following definitions of incidence have been used:
Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, <1/1,000), and very rare (< 1/10,000). The data include also reports of isolated cases.

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<th>System Organ Class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt;1/10)</th>
<th>Uncommon (≥ 1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10 000 to &lt;1/1000)</th>
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<td>Thrombocytopenia, agranulocytosis</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Nervousness, anxiety, impotence</td>
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<td>Nervous system disorders</td>
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<td>Dizziness, headache</td>
<td>Paraesthesia, muscle weakness and cramps</td>
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<td>Blurred visual, dry and/or irritated eyes, conjunctivitis</td>
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<td>Ear and labyrinth disorders</td>
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<td>Tinnitus, reversible hearing loss</td>
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<td>Cardiac disorders</td>
<td>Bradycardia, hypotension and postural disorders (very rarely with syncope), palpitations, cold hands and feet</td>
<td>Deterioration of heart failure, cardiogenic shock at patient with acute myocardial infraction*, first degree AV block, edema, and pericardial pain</td>
<td>Conduction disturbances, various types of arrhythmia</td>
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<td>Rare (≥1/10 000 to &lt;1/1000)</td>
<td>Very Rare (&lt;1/10000)</td>
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<td>Vascular disorders</td>
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<td>Gangrene in patients with severe peripheral circulatory disorder</td>
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<td>Dyspnoea on exertion</td>
<td>Bronchospasm s, including in patients without obstructive pulmonary abnormalities</td>
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<td>Hepatitis</td>
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<td>Photosensitivity, deterioration in psoriasis</td>
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<td></td>
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<td>Dysgeusia (Taste disturbances)</td>
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</table>

*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: 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.
4.9 Overdose

Symptoms

The symptoms of overdose may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include:

Close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta adrenoceptor stimulant (dobutamine, isoprenaline, noradrenaline) may be given. Dobutamine can be administered at 2.5 to 10 micrograms/kg/minute by intravenous infusion.

Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Administration of calcium ions may also be considered. Bronchospasm can usually be reversed by bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Metoprolol is a competitive β₁-selective beta blocker: it blocks β₁ receptors at dosages that are much lower than those necessary to block β₂ receptors.

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.

Metoprolol has a non-significant membrane-stabilising effect and displays no partial agonist activity. Metoprolol reduces or inhibits the agonist effect of catecholamines on the heart. 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 absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.
Distribution
The medicinal product is approx. 5–10% bound to plasma proteins.

Metabolism and elimination
Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute.

Special population
Elderly:
In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients shows 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 are 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
Cellulose, microcrystalline (E460)
Gelatin (E441)
Sodium starch glycolate
Silica, colloidal hydrated (E551)
Stearic acid

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Tablets are packed in PVC/Aluminium blisters containing 10, 20, 28, 30, 50, 56, 60, 84 and 90 tablets. Not all pack sizes may be marketed.

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
Intas Pharmaceuticals Limited
Sage House, 319, Pinner Road
North Harrow
Middlesex HA 1 4 HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 30139/0017
PL 30139/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2011

10 DATE OF REVISION OF THE TEXT
23/09/2011
Module 3
Patient Information Leaflet

are used to help the heart pump more strongly
• if you are suffering from heart rhythm problems known as sick sinus syndrome
• if you have or have had breathing difficulties or asthma
• if you are suffering from untreated high blood pressure due to a tumour near the kidney (phaeochromocytoma)
• if you are suffering from increased acidity of the blood (metabolic acidosis)
• if you are receiving verapamil or diltiazem by intravenous injection,
• If you have very low blood pressure

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow his advice.

Take special care with Metoprolol Tartrate tablets
It is important to tell your doctor before taking Metoprolol Tartrate tablets
• if you want to discontinue treatment: you should not stop suddenly, as this can aggravate chronic heart failure and increase the risk of a heart attack.
• If you have breathing problems.
• If you get allergic reactions, for example to insect stings, foods or other substances,
• if you have diabetes. Metoprolol can mask some symptoms of low blood sugar in diabetics. It may also be necessary to adjust any treatment with blood sugar reducing agents that you already receive.
• If you have poor blood circulation or heart failure.
• If you have a slow heartbeat.
• If you have to undergo an operation, please tell your anaesthetist that you are taking Metoprolol Tartrate tablets.
• If you have severe liver problems.
• If you have a tumour near the kidney (phaeochromocytoma)
• If you have a type of chest pain called Prinzmetal's angina.

propafenone, amiodarone and quinidine.
• Atropine (used for treating certain eye conditions)
• Adrenaline (used for emergency treatment of allergic reactions).
• Anaesthetics.
• Medicines used to treat diabetes
• Lidocaine (used to treat abnormal heart rhythm).
• Baclofen (used to treat spastic conditions).
• Mefloquine (used in malaria).
• Antacids (used for stomach upsets)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Taking Metoprolol Tartrate tablets with food and drink
You should minimise your alcohol intake when taking this medicine as it may increase the effect of metoprolol.

Pregnancy and breast-feeding

Pregnancy
Metoprolol Tartrate is not generally recommended during pregnancy although your doctor may decide to use metoprolol in late pregnancy under close supervision including any effects on the newborn infant.

Please inform your doctor if you are pregnant.

Breast-feeding
Breast-feeding should generally be discontinued during treatment with metoprolol although your doctor may decide to use metoprolol in a nursing mother with close supervision of the infant.

Ask your doctor or pharmacist for advice before taking any medicine.
1. What Metoprolol Tartrate tablets are and what they used for

The active ingredient, metoprolol tartrate, belongs to a group of drugs called beta blockers.

Metoprolol tartrate has an effect on how the heart works and reduces blood pressure. Metoprolol tartrate can be used to treat a number of conditions. It can be prescribed to patients:
- to reduce high blood pressure
- with chest pain due to angina
- with fast or irregular heart rhythm
- who have had a heart attack, as protection against a possible further heart attack
- to prevent migraines

Metoprolol is for use in adults.

2. Before you take Metoprolol Tartrate tablets

Do not take Metoprolol Tartrate tablets
- if you are allergic (hypersensitive) to metoprolol or any of the other ingredients in this medicine (see section 6: Further information)
- if you are allergic to a group of drugs called beta blockers.
- if you have a condition affecting the conduction of electrical impulses in the heart (second and third degree heart block)
- if you have severe heart failure
- if you are suffering from shock, due to your heart not pumping properly
- if you have seriously poor circulation
- if you have a very slow heart rate (less than 50 beats per minute)
- if you are receiving group of drugs called beta-agonists which

- If you have an overactive thyroid (symptoms such as increased heart rate, sweating, tremor, anxiety, increased appetite or weight loss may be hidden by this medicine)
- If you have or have suffered from skin rashes called psoriasis
- If you suffer from dry eyes

Consult your doctor if one of the above warnings applies to you, or has done so in the past.

Taking other medicines

Metoprolol Tartrate tablets can affect how some other medicines work, and some medicines also affect how metoprolol works.

If Metoprolol Tartrate tablets are to be combined with the medicines listed below, you must consult your doctor:
- Medicines used to lower blood pressure including
  - Calcium antagonists e.g. verapamil, nifedipine and diltiazem
  - Centrally acting agents e.g. clonidine, guanfacine, mexitridine, methyldopa, and nimodipine
- Alpha blockers e.g. prazosin, tamsulosin, terazosin, doxazosin

The effects of metoprolol and other blood pressure lowering drugs on blood pressure are usually additive.
- Rifampicin (used in tuberculosis)
- Medicine used to treat allergies (antihistamines)
- Medicines used to treat depression (antidepressants)
- Medicines used to treat serious mental illness (antipsychotics)
- Medicines used to reduce inflammation and fever for example celecoxib, ibuprofen and ibuprofen.
- Other beta blocker medicines similar to metoprolol including those in the form of eye drops such as timolol.
- Ergotamine (used in migraine)
- Nitrates such as nitroglycerine (used in angina)
- Narcotics such as oxycodone (used to control severe pain)
- Digitals glycosides such as digoxin (used in heart failure).
- Medicines used to treat abnormal heart rhythm such as

Driving and using machines

Metoprolol may influence your ability to drive and use machines because it may cause dizziness and fatigue. This applies to a greater extent at the beginning of treatment. Do not drive or use any tools or machines if side effects such as fatigue or dizziness occur.

3. How to take Metoprolol Tartrate tablets

Always take Metoprolol Tartrate tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The tablets should be swallowed on an empty stomach. The usual dose is:
- in the case of high blood pressure (hypertension): 100 or 200 mg, preferably once a day, as a single dose in the morning, or in divided doses (morning and evening). Your doctor may ask you to start with a lower dose.
- in the case of chest pain (angina) depending on the symptoms 100 to 200 mg per day, in divided doses (morning and evening). Your doctor may ask you to start with a lower dose.
- in the case of abnormal heart rhythm: 100 to 150 mg per day, in divided doses (in the morning and in the evening). If necessary, your doctor can increase your dosage further.
- as protection against a further heart attack: 100 mg twice a day (in the morning and in the evening).
- to prevent migraines: 100 to 200 mg per day, in divided doses, in the morning and evening.

This medicine is generally taken for long-term. Never change the dosage yourself.

The dose may be reduced in patients with severe liver problems.
The tablet can be divided into equal doses.

Use in children: Metoprolol Tartrate tablets are not recommended for children.

If you take more Metoprolol Tartrate tablets than you should
Symptoms of overdose include a low blood pressure, slow heart beat, shortness of breath, dizziness, fatigue, cough, wheezing and, in severe cases, cardiac arrest. Contact your doctor immediately. Take with you the empty packs of the medicines you consumed. Sometimes, hospitalisation may be necessary.

If you forget to take Metoprolol Tartrate tablets
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Metoprolol Tartrate tablets
Never suddenly stop taking Metoprolol Tartrate tablets. If you suddenly stop the medicine, then your physical condition may deteriorate immediately, abnormalities in your heart rhythm may develop or you may develop high blood pressure. Discontinuing metoprolol treatment should always be undertaken in consultation with your doctor who will direct you how to gradually reduce the dose until the treatment is stopped altogether.
If you suffer problems during the tapering-off period, consult your doctor.

- diarrhea
- constipation

Uncommon:
- an increase in weight
- depression
- reduced alertness
- drowsiness
- difficulty in sleeping
- nightmares
- abnormal skin sensations (tingling, tickling, itching or burning)
- muscle weakness and cramps
- an aggravation of heart failure
- water retention
- chest pain
- wheezing
- vomiting
- skin rash
- increased sweating

Rare:
- nervousness
- anxiety
- difficulty or loss of interest in sex
- eye problems (blurred vision, dry and/or irritated eyes, inflammation)
- runny nose
- dry mouth
- abnormal blood test results of liver function
- reversible hair loss

6. Further information

What Metoprolol Tartrate tablets contains
The active substance is Metoprolol tartrate.

Each tablet contains 50/100 mg Metoprolol tartrate.

The other ingredients are:
Cellulose microcrystalline (E460), Gelatin (E441), Sodium starch glycolate, Silica colloidal hydrated (E551), Stearic acid

What Metoprolol Tartrate tablets looks like and contents of the pack
50 mg tablets: White to off-white, approximately 8 mm round, biconvex tablet marked ☒ on one side and a scoreline on the other side.
100 mg tablets: White to off-white, approximately 10 mm round, biconvex tablet marked ☒ on one side and a scoreline on the other side.

Metoprolol Tartrate tablets are available in PVC/ Aluminium blister packs containing 10, 20, 28, 30, 50, 56, 80, 84 and 90 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation holder
Intas Pharmaceuticals Limited,
Sage House, 319, Pinner Road, North Harrow, Middlesex
HA1 4HF, United Kingdom
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Metoprolol Tartrate tablets can cause side effects, although not everybody gets them.

Stop treatment and contact a doctor at once if you have the following symptoms of:

- an allergic reaction such as itching, difficulty breathing or swelling of the face, lips, throat or tongue.
- very slow heart and blood pressure (you may feel very dizzy or weak) or in case of breathing difficulties.

The following terms are used to describe how often side effects have been reported:

- Very common: affects 1 or more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000

Very common:
- fatigue

Common:
- dizziness
- headache
- slow heart rate
- low blood pressure which might make you faint or dizzy particularly when standing up quickly from a sitting or lying position
- irregular heart beat
- poor blood circulation which makes the toes and fingers numb and pale
- Shortness of breath on exertion
- feeling sick
- abdominal pain

Very rare:
- severe reduction in number of white blood cells which makes infections more likely
- reduction in blood platelets, which increases risk of bleeding or bruising
- change in levels of blood fats
- low blood sugar in diabetics taking insulin
- memory impairment
- confusion
- hallucination
- personality changes
- ringing in the ears
- reversible hearing loss
- gangrene
- taste disorders
- inflammation of liver (hepatitis)
- hypersensitivity to light
- deterioration in psoriasis
- joint pain
- abnormal curvature of the penis

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Metoprolol Tartrate tablets

- Keep out of the reach and sight of children.
- Do not use Metoprolol Tartrate tablets after the expiry date, which is stated on the blister and the carton after "EXP". The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Module 4

Labelling

Metoprolol Tartrate 50 mg tablets - PL 30139/0017

Carton – pack size 28
PAR Metoprolol Tartrate 50 mg and 100 mg tablets

PL 30139/0017-18; UK/H/4414/001-2/DC

Carton – pack size 56

Any unused product or waste material should be disposed of in accordance with local requirements.

PL Holder: Intas Pharmaceuticals Limited
Sage House, 319 Pinner Road,
North Harrow, Middx.
HA1 4HF, United Kingdom

Each tablet contains Metoprolol tartrate 50 mg. Please see enclosed leaflet.

50 mg

Keep area blank & varnish free for overcoding Lot and EXP.

Keep out of the reach and sight of children.
Do not store above 25°C.
Metoprolol Tartrate 50 mg and 100 mg tablets

Braille translation

Metoprolol Tartrate #50 mg tablets

Blister foil
Metoprolol Tartrate 100 mg tablets - PL 30139/0018

Carton – pack size 28
Carton – pack size 56
PAR Metoprolol Tartrate 50 mg and 100 mg tablets

Braille translation

Metoprolol Tartrate #100 mg tablets

Blister foil

Space for embossed batch details

EXF. LOT.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Intas Pharmaceuticals Limited Marketing Authorisations for the medicinal products Metoprolol Tartrate 50 mg and 100 mg tablets (PL 30139/0017 and 0018; UK/H/4414/001-2/DC) on 23rd September 2011. The products are prescription-only medicines.

These are generic applications for Metoprolol Tartrate 50 mg and 100 mg tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Betaloc Tablets 50mg and 100mg (PL 17901/0109 and 0108), licensed to AstraZeneca UK Ltd. The cross-referenced products were originally authorised to Astra Pharmaceuticals Limited (PL 00017/0073R and 0074R) on 18th August 1988 and underwent Change of Ownership (CoA) procedures to the current AstraZeneca UK Ltd licences on 28th May 2002. The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Intas Pharmaceuticals Limited applied for Marketing Authorisations for Metoprolol Tartrate 50 mg and 100 mg tablets in Bulgaria, Czech Republic, France, Germany, Italy, Poland and Romania.

Metoprolol tartrate is a competitive cardioselective β-adrenoceptor blocking agent. Metoprolol is a β-adrenoceptor antagonist selective for cardiac β1-receptors without partial agonist (sympathomimetic) activity. It blocks β1 receptors at dosages that are much lower than those necessary to block β2 receptors. A negative chronotropic effect on the heart is a consistent feature of metoprolol administration. Thus, cardiac output and systolic blood pressure rapidly decrease following acute administration.

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.

Metoprolol Tartrate 50 mg and 100 mg tablets are indicated in adults for:

- Hypertension
- Angina pectoris
- Tachyarrhythmias, in particular supraventricular tachycardia
- Maintenance treatment after a myocardial infarction
- Prophylaxis of migraine

The medicinal products are in a tablet form, which dissolves rapidly and results in a rapid and complete absorption after oral administration with peak plasma concentrations occurring 1.5 - 2 hours after dosing. The plasma concentrations increase in a linear manner in relation to dosage (within the therapeutic dosage range). Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by approximately 30–40%. The active substance, metoprolol, is
approximately 5–10% bound to plasma proteins. Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. Elimination is mainly via hepatic metabolism (>90%). Terminal half life is about 3–4 hours.

Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk. It 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 phenotype. Approximately 7% of Caucasians and less than 1% Orientals are poor metabolisers. CYP2D6 poor metabolisers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolisers with normal CYP2D6 activity. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Metoprolol Tartrate 100 mg tablets, to that of the reference product, Betaloc Tablets 100mg (AstraZeneca UK Ltd). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Metoprolol Tartrate 50 mg tablets  
Metoprolol Tartrate 100 mg tablets |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Metoprolol tartrate</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code) | Beta blocking agents, selective  
(C07AB02) |
| Pharmaceutical form and strength(s)          | Tablets  
50 mg, 100 mg |
| Reference numbers for the Decentralised Procedure | UK/H/4414/001-2/DC |
| Reference Member State                       | United Kingdom |
| Member States concerned                      | UK/H/4414/001/DC: BG, CZ, DE, FR, PL and RO  
UK/H/4414/002/DC: BG, CZ, DE, FR, IT, PL and RO |
| Marketing Authorisation Number(s)            | PL 30139/0017 and 0018 |
| Name and address of the authorisation holder  | Intas Pharmaceuticals Limited  
Sage House, 319, Pinner Road  
North Harrow  
Middlesex HA 1 4 HF  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Metoprolol Tartrate

Nomenclature:

INN: Metoprolol tartrate
Chemical names: Bis[(2RS)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol][2R,3R]-2,3-dihydroxybutanedioate

Structure:

\[
\begin{array}{c}
\text{HO}_2\text{C} \\
\text{OH} \\
\text{H} \\
\text{H}_2\text{C} \\
\text{O} \\
\text{OH} \\
\text{and enantiomer} \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\]

Molecular formula: \((\text{C}_{13}\text{H}_{25}\text{NO}_3)_2\cdot\text{C}_4\text{H}_6\text{O}_6\)
Molecular weight: 684.81 g/mol
CAS No: 56392-17-7
Physical form: White or almost white, crystalline powder or colourless crystals
Solubility: Very soluble in water, freely soluble in alcohol

The active substance, metoprolol tartrate, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of metoprolol tartrate are supported by European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of metoprolol tartrate for inclusion in these medicinal products.

The CEP specifies that the retest period of the active substance is 5 years, when stored, protected from light, in a container consisting of double polythene bags, inside a fibreboard container.
MEDICINAL PRODUCT

Description and Composition

Metoprolol Tartrate 50 mg and 100 mg tablets are presented as white to off-white, round, biconvex, tablets marked with D (50 mg) or E (100 mg) on one side and a scoreline on the other side. The tablet can be divided into equal halves. Each tablet contains 50 mg or 100 mg of the active ingredient, metoprolol tartrate.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose (E460), gelatin (E441), sodium starch glycolate, colloidal hydrated silica (E551) and stearic acid. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The stearic acid has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin supplier stating that the gelatin it provides complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Betaloc Tablets 50mg and 100mg (PL 17901/0109 and 0108, AstraZeneca UK Ltd).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System
The medicinal products are licensed for marketing in PVC (polyvinylchloride) / aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 10, 20, 28, 30, 50, 56, 60, 84 and 90 tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 2 years, with the storage instructions ‘Do not store above 25°C’.

Quality Overall Summary
A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The user-testing of the PIL has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion
All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Metoprolol Tartrate 50 mg and 100 mg tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of metoprolol tartrate, a widely used and well-known active substance. The overview, dated September 2009, cites 28 references from the published literature dated up to year 2008. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Betaloc Tablets 50mg and 100mg (PL 17901/0109 and 0108, AstraZeneca UK Ltd).

There are no objections to approval of Metoprolol Tartrate 50 mg and 100 mg tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Metoprolol Tartrate 50 mg and 100 mg tablets are indicated in adults for:

- Hypertension
- Angina pectoris
- Tachyarrhythmias, in particular supraventricular tachycardia
- Maintenance treatment after a myocardial infarction
- Prophylaxis of migraine

The indications are consistent with those for the UK reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is satisfactory.

TOXICOLOGY

The toxicology of metoprolol tartrate is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of metoprolol tartrate is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Metoprolol Tartrate 100 mg tablets, to that of the reference product, Betaloc Tablets 100mg (AstraZeneca UK Ltd). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-way, two-treatment, two-period, two-sequence, single-dose crossover bioequivalence study conducted in 28 healthy adult male human subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally, with 240 ml of water, to each
subject in each period. A satisfactory washout period of 4-8 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of metoprolol were detected by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for this study were \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \).

**Results:**

28 subjects were enrolled in the study; 26 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 2 subjects was satisfactorily justified.

**Safety** – There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for metoprolol for a randomised, two-treatment, two-period, two-sequence, single-dose crossover study; n=26 healthy subjects, dosed fed; \( t=24 \) hours; washout period: 4-8 days

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>In-transformed Geometric Least Squares Mean</th>
<th>Ratio (B/A) %</th>
<th>90% Confidence Interval (Parametric)</th>
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<tbody>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>126.493</td>
<td>134.130</td>
<td>94.3%</td>
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<tr>
<td>AUC(_{0-t}) (ng h/mL)</td>
<td>838.111</td>
<td>886.291</td>
<td>94.6%</td>
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<tr>
<td>AUC(_{0-\infty}) (ng h/mL)</td>
<td>863.709</td>
<td>912.070</td>
<td>94.7%</td>
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</table>

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) for metoprolol fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Metoprolol Tartrate 50 mg tablets. As Metoprolol Tartrate 50 mg and 100 mg tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 100 mg strength can be extrapolated to the 50 mg strength tablets.

**Clinical efficacy**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of metoprolol tartrate is well-established from its extensive use in clinical practice.
Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of metoprolol tartrate is well-known.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user-testing has been assessed and accepted.

Labelling
The labelling is satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview cites 48 references from the published literature dated up to year 2008. The CV of the clinical expert has been supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Metoprolol Tartrate 50 mg and 100 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Metoprolol Tartrate 100 mg tablets and the UK reference product, Betaloc Tablets 100mg (AstraZeneca UK Ltd).

As the proposed products, Metoprolol Tartrate 50 mg and 100 mg tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 100 mg strength were extrapolated to the 50 mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the UK reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Metoprolol Tartrate 50 mg and 100 mg tablets are generic versions of the reference products, Betaloc Tablets 50mg and 100mg (PL 17901/0109 and 0108, AstraZeneca UK Ltd). Extensive clinical experience with metoprolol tartrate is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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