Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metoprolol 50 Stada Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Metoprolol tartrate 50 mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat tablet, scored on one side.
Approximate dimensions: diameter 8 mm x height 3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hypertension and angina pectoris.
- Cardiac arrhythmias, especially supraventricular tachyarrhythmias.
- Adjunct to treatment of thyrotoxicosis.
- Early intervention with Metoprolol in acute myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics.
- Metoprolol has been shown to reduce mortality when administered to patients with acute myocardial infarction.
- Prophylaxis of migraine.

4.2 Posology and method of adminstration

For oral use only.

Metoprolol 50 Stada tablets should be swallowed whole; not chewed.

The dose must always be adjusted to suit the individual needs of each patient but should not exceed 400mg daily. The following are guidelines:

Adults:
Hypertension: The starting dose is 100 mg in the morning taken either in single or divided doses. Depending on the patient's response, the dosage may be increased to 200 mg daily taken in single or divided doses. Most patients may be expected to respond rapidly and satisfactorily within this dosage range. Further antihypertensive effect may be achieved by the addition of an antihypertensive diuretic or other hypotensive agent.

Metoprolol 50 Stada may prove beneficial when administered in patients with previously untreated hypertension; and in whom the response to previous therapy was inadequate. Previous therapy may be continued, and Metoprolol 50 Stada added into the regime with adjustment of the concurrent therapy if necessary.

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

dose of 50 - 100 mg twice daily.

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

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

Myocardial infarction: Early intervention.
Therapy should start with 50 mg every 6 hours for 48 hours, preferably within 12 hours of the onset of chest pain.

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

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

Elderly:
Whilst there is no evidence to suggest that dosage requirements are different in otherwise healthy elderly patients, caution is indicated as an excessive decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Hepatic impairment:
The lower dosage recommendations are more appropriate in patients with significant hepatic dysfunction.

Children:
Not recommended.

4.3 Contraindications

Known sensitivity to Metoprolol and related derivatives, atrioventricular block of second or third degree, uncontrolled heart failure, clinically relevant sinus bradycardia, sick-sinus syndrome, severe peripheral arterial disease, cardiogenic shock.

Metoprolol is also contra-indicated when myocardial infarction is complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100 mmHg) and/or severe heart failure.

Use in patients with asthma or a history of asthma.

4.4 Special warnings and special precautions for use

Metoprolol may aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the patient develops increasing bradycardia, Metoprolol 50 Stada should be given in lower doses or gradually withdrawn.

Abrupt cessation of therapy with a beta-blocker should be avoided. When possible, Metoprolol 50 Stada should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. During its withdrawal the patient should be kept under close surveillance.

Although cardioselective beta-blockers may have less effect on lung function than non selective beta-blockers, they should as with all beta-blockers be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Therapy with a $beta_2$- stimulant may become necessary or current therapy may require adjustment.

Metoprolol 50 Stada may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol 50 Stada may mask some of the symptoms of thyrotoxicosis and of hypoglycaemia by inhibition of sympathetic nerve functions.

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

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

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

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

Metoprolol 50 Stada should be administered with caution to patients with metabolic acidosis.

Metoprolol 50 Stada therapy should be brought to the attention of the anaesthetist prior to general anaesthesia. In a patient under beta-blockade, the anaesthetic selected should be one exhibiting as little negative inotropic activity as possible (halothane/nitrous oxide).

Patients with pre-existing severe renal insufficiency have in isolated cases experienced reduced kidney function. Metoprolol treatment should be accompanied by kidney function monitoring.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of Metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension. As with all beta blockers particular caution is called for when Metoprolol is administered together with prazosin for the first time. However, combinations of antihypertensive drugs may often be used beneficially to improve control of hypertension.

Metoprolol can reduce myocardial contractility and impair intracardiac conduction. Care should be exercised when drugs with similar activity e.g. antiarrhythmic agents, general anaesthetics, are given concurrently. Concurrent treatment of Metoprolol and Verapamil type or diltiazem type Calcium Channel Blockers or other anti arrhythmics have increased risks of hypotension, bradycardia and other cardiac arrhythmias (including asystole).
Care should also be exercised when beta-blockers are given in combination with sympathetic ganglion blocking agents; other beta-blockers (also in the form of eye drops); or MAO inhibitors.

If combination treatment with clonidine is to be discontinued Metoprolol should be withdrawn several days before clonidine.

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

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.

Concurrent use of Metoprolol and sympathomimetics (adrenaline, noradrenaline) – which may be contained in cough remedies, nasal and eye drop preparations) may produce a significant increase in blood pressure.

Metoprolol is metabolised mainly by Cytochrome P450 (CYP) 2D6. Therefore, enzyme inducing agents (e.g. rifampicin) may reduce plasma concentration of Metoprolol, whereas enzyme inhibitors that interact with Metoprolol (e.g. cimetidine) may increase plasma concentrations of Metoprolol.

Bupropion and dextropropoxyphene (both enzyme inhibitors) have been reported to interact with Metoprolol.

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

Metoprolol may impair the elimination of lignocaine.

Indomethacin may reduce the antihypertensive effect of beta-blockers.

Nitroglycerin may enhance the hypotensive effect of Metoprolol.

4.6 Pregnancy and lactation

Metoprolol 50 Stada is not recommended for use in pregnancy or lactation unless in the opinion of the physician the expected benefit outweighs the possible risk to the foetus/infant.

Metoprolol has been used in pregnancy associated hypertension under close supervision after 20 weeks gestation.

Metoprolol crosses the placental barrier and is present in umbilical cord blood, however no evidence of foetal abnormalities has 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.

The amount to Metoprolol ingested via breast milk appears to be negligible with regard to its beta-blocking effects when the dose administered to the mother is within the therapeutic range.

If Metoprolol is used during pregnancy and lactation, the foetus, neonate or breast-fed infant should be closely observed for undesirable effects due to the drug's beta-blocking action (e.g. bradycardia, hypoglycaemia).

4.7 Effects on ability to drive and use machines

As with all beta-blockers, Metoprolol may affect the patient’s ability to perform skilled tasks. Patients should be warned not to drive or operate machinery until they are sure they are not affected.

4.8 Undesirable effects

Central and peripheral nervous system: Occasionally fatigue, dizziness, headache. Rarely paraesthesiae, muscle cramps, depression, decreased mental alertness, somnolence or insomnia, nightmares. In isolated cases: personality disorder, hallucinations.

Cardiovascular system: Occasionally bradycardia, postural disorders (occasionally with syncope). Rarely heart failure, cardiac arrhythmias, oedema, palpitation, Raynaud's phenomenon. In isolated cases: disturbances of cardiac conduction, precordial pain, gangrene in patients with pre-existing severe peripheral circulatory disorders.

Gastro-intestinal tract: Occasionally nausea and vomiting, abdominal pain. Rarely diarrhoea or constipation. In isolated cases: dryness of the mouth, liver function test abnormalities, hepatitis.

Skin and appendages: Rarely skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), occurrence of antinuclear antibodies (not associated with SLE). In isolated cases: photosensitivity, increased sweating, loss of hair.

Respiratory tract: Occasionally exertional dyspnoea. Rarely bronchospasm, also in patients without a history of obstructive lung disease. In isolated cases: rhinitis.

Endocrine system and metabolism: In isolated cases: weight gain.

Urogenital system: There are isolated reports of disturbances of libido and potency.

Sense Organs: In isolated cases: disturbances of vision, dry and/or irritated eyes, tinnitus, in doses exceeding those recommended loss of hearing.

Blood: In isolated cases: thrombocytopenia.

Other organ systems: In isolated cases: arthritis.

The reported incidence of skin rashes and/or dry eyes associated with the use of beta-blockers is small and in most cases the symptoms have cleared when treatment was withdrawn. Consideration should be given to discontinuation of the drug if any such reaction is not otherwise explicable.

4.9 Overdose

Signs: Metoprolol overdosage may lead in more severe cases to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and occasionally hyperkalaemia. The first manifestations usually appear 20 minutes to 2 hours after drug ingestion.

Treatment: Treatment should include close monitoring of cardiovascular, respiratory and renal functions; and blood glucose and electrolytes. Further absorption may be prevented by induction of vomiting, gastric lavage or administration of activated charcoal if ingestion is recent. Cardiovascular complications should be treated symptomatically which may require the use of sympathomimetic agents (e.g. noradrenaline, metaraminol), atropine or inotropic agents (e.g. dopamine, dobutamine). Temporary pacing may be required for AV block. Glucagon can reverse the effects of excessive beta-blockade given in a dose of 1-10mg intravenously. Intravenous $beta_2$-stimulants may be required to relieve bronchospasm. Metoprolol cannot be effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Betablocking agents, selective. ATC code: C07AB02.

Metoprolol is a cardioselective beta-adrenergic receptor blocking agent. It has a relatively greater blocking effect on $beta_1$-receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on $beta_2$-receptors, which are chiefly involved in broncho- and vasodilation.

5.2 Pharmacokinetic properties

Metoprolol is well absorbed after oral administration, with peak plasma concentrations occurring after 1.5-2 hours. The bioavailability of a single dose is approximately 50%, increasing to approximately 70% during repeated administration.

Elimination is mainly by hepatic metabolism and mean 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.

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

5.3 Preclinical safety data

Reproductive effects:
Rat Oral TDL_O: 60 gm/kg; Effects on newborn (Live birth index; weaning or lactation index)
Toxicity data:
Mouse i.v. LD50: 62 mg/kg No toxic effect noted
Mouse Oral LD50: 1050 mg/kg No toxic effect noted
Woman Oral TDL_O: 150 mg/kg; Sense organs and special senses (mydriasis); Behavioural (sleep); Cardiac (change in force of contraction)
Registry of Toxic Effects 1993

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone
Croscarmellose sodium
Magnesium stearate
Talc
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

AL/PVC/PVDC blisters.
Pack sizes: 10, 20, 28, 50, 56, 84 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastraβe 2-18
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th March 2000
Date of last renewal: 20th March 2005

10 DATE OF REVISION OF THE TEXT

August 2005