Professional information

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

BETACOR® 5 film-coated tablets

BETACOR® 10 film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BETACOR 5 film-coated tablet contains 5 mg bisoprolol fumarate.

Each BETACOR 10 film-coated tablet contains 10 mg bisoprolol fumarate.

Sugar free

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

BETACOR 5 are yellowish white, heart-shaped biconvex film-coated tablets with dividing score on both sides.

BETACOR 10 are pale-orange light-orange, heart-shaped biconvex film coated tablets with dividing score on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BETACOR is indicated for the management of mild to moderate essential hypertension and angina pectoris. It may be used alone or in combination with other antihypertensive medicines.

4.2 Posology and method of administration

Posology

In all cases the dosage should be adjusted individually, in particular according to the pulse rate and therapeutic success.

Hypertension

The recommended dosage is 5 mg BETACOR once daily.

If necessary, the dosage may be increased to 10 mg once daily. Individual patients may benefit from a dose of 20 mg once daily.

The maximum recommended dosage is 20 mg once daily.

Angina pectoris

The recommended dosage is 5 mg BETACOR once daily.

If necessary, the dosage may be increased to 10 mg once daily.

No benefit was shown by increasing the dose to 20 mg once daily.

The maximum recommended dosage is 20 mg once daily.

Dosage in hepatic and/or renal insufficiency

In patients with liver or kidney function disorders of mild to moderate severity no dosage adjustment is normally required. In patients with severe kidney function disorders (creatinine clearance < 30 ml/min) and in patients with severely impaired liver function a daily dose of 10 mg BETACOR should not be exceeded.

There is only limited experience with the use of BETACOR in dialysis patients. There are no indications of the necessity to alter the dose regimen.

Elderly people

No dose adjustment is required in elderly patients.

Children

There is no therapeutic experience with BETACOR in children. Its use in children is therefore not recommended. (See section 4.4).

Method of administration

The film-coated tablets are to be swallowed whole in some liquid in the morning before, during or after breakfast.

The duration of treatment is not limited. It depends upon the nature and severity of the disease. BETACOR therapy should not be stopped abruptly, particularly not in patients with ischaemic heart disease, as this may lead to acute deterioration of the patient's state of health (see section 4.4). If discontinuation of therapy becomes necessary, the dose should be gradually reduced (e.g. halving of the dose at weekly intervals).

4.3 Contraindications

BETACOR is contra-indicated in patients with

- hypersensitivity to bisoprolol or to any of the excipients (see section 6.1)
- acute heart failure or during episodes of heart-failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia or pulse rate (PR) below 50 beats per minute
- symptomatic hypotension
- severe bronchial asthma
- peripheral arterial occlusive disease and Raynaud's syndrome
- phaeochromocytoma before full alpha blockade is achieved (see section 4.4)
- metabolic acidosis

- pregnancy (see Pregnancy and lactation.)

4.4 Special warnings and precautions for use

Treatment with BETACOR must not be withdrawn abruptly unless clearly indicated, since abrupt withdrawal of bisoprolol (as in BETACOR) may lead to an acute deterioration of the patient's condition in particular in patients with ischaemic heart disease (see section 4.2). Discontinuation should be gradual, and patients should be advised to limit the extent of their physical activity during the period in which the medicine is being discontinued.

Caution is warranted when treating patients with hypertension or angina pectoris and concomitant heart failure with BETACOR.

BETACOR may be used only with special caution in:

- Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) may be masked.
- Strict fasting
- Ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect.
- First degree AV block
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Despite its high $beta_1$-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina. Utmost caution must be exercised.
- Peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy)

  BETACOR may aggravate the symptoms of peripheral arterial occlusive disease (PAOD) or Raynaud's syndrome (due to unopposed arteriolar alpha-sympathetic activation).

  Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Digitalisation of patients receiving long-term BETACOR therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

Clonidine

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines, which may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.

Psoriasis

Patients with psoriasis or with a history of psoriasis may have their conditions worsened by BETACOR.

Hyperthyrodism

The symptoms of hyperthyroidism may be masked under treatment with BETACOR.

Thyrotoxicosis

The symptoms of thyrotoxicosis may be masked under treatment with BETACOR.

Pheochromocytoma

In patients with phaechromocytoma BETACOR must not be administered until after full alpha-receptor blockade has been established. Beta blockade is seldom required in the pre-operative preparation of these patients.

Children

Safety and efficacy of BETACOR have not been established in children.

General Anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradydysrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Asthma and Chronic Obstructive Pulmonary Disease

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than nonselective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, BETACOR may be used with caution. In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore, the dose of $beta_2$-stimulants may have to be increased.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

- *Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type:*
  Negative effect on contractility and atrio ventricular conduction. Intravenous administration of verapamil in patients on BETACOR treatment may lead to profound hypotension and atrioventricular block.

- *Centrally acting antihypertensive medicines (e.g. clonidine, methyldopa, moxonodine):* Concomitant use of BETACOR and centrally acting antihypertensive medicines may lead to a further reduction in heart rate and cardiac output and to vasodilation. Beta-blockers (e.g. BETACOR) may exacerbate the “rebound hypertension” which can occur in case of abrupt withdrawal of centrally acting antihypertensive medicines (e.g. Clonidine). If the two medicines are co-administered, the β-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped.

Combinations to be used with caution

- *Calcium channel antagonists of the dihydropyridine type (e.g. nifedipine, amlodipine):* Concomitant use of BETACOR and dihydropyridine calcium channel antagonists may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
- *Class-III antidysrhythmic medicines (e.g. amiodarone):* Effect on atrio-ventricular conduction time may be potentiated.
- *Class I antiarrhythmics (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone):* Effect on atrio-ventricular conduction time and negative inotropic effect may be increased.
- *Parasympathomimetic medicines:* Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- *Topical beta-blockers (e.g. eye drops for glaucoma treatment)* may add to the systemic effects of BETACOR.
- *Insulin and oral antidiabetic medicines:* Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia (see section 4.4).
- *Anaesthesia:* Attenuation of the reflex tachycardia and increase of the risk of hypotension.
- *Digoxin:* Decrease in heart rate, lengthening of atrio-ventricular conduction time.

- *Non-steroidal anti-inflammatory drugs (NSAIDs):* NSAIDs may reduce the hypotensive effect of BETACOR.
- *Beta-sympathomimetics (e.g. dobumamine):* Combination with BETACOR may reduce the effect of both agents. Higher doses of epinephrine (adrenaline) may be necessary for treatment of allergic reactions.
- *Sympathomimetics that activate both beta- and alpha-adrenoceptors [e.g. norepinephrine (noradrenaline), epinephrine (adrenaline)]:* Combination with BETACOR may unmask the alpha-adrenoceptor-mediated vasoconstrictor effect of these medicines leading to blood pressure increase and exacerbated intermittent claudication.
- *Concomitant use with other antihypertensive medicines or with other medicinal products with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines)* may increase the risk of hypotension.

Combinations to be considered

- *Mefloquine:* Increased risk of bradycardia.
- *Monoamine oxidase inhibitors (except MAO-B inhibitors):* Enhanced hypotensive effect of the beta-blockers but also risk of hypertensive crisis.
- *Rifampicin:* Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.
- *Ergotamine derivatives:* Exacerbation of peripheral circulatory disturbances. In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy

BETACOR has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn.

BETACOR reduces placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia, hypotonia, bradycardia and cardiovascular collapse) may occur in the foetus and newborn infant.

Lactation

It is not known whether BETACOR is excreted in human milk. Therefore, mothers on treatment with BETACOR should not breastfeed their infants.

Fertility

No effect on fertility was observed in male or female rats treated with bisoprolol at oral doses up to 150 mg/kg/day.

4.7 Effects on ability to drive and use machines

Bisoprolol, as contained in BETACOR, may cause dizziness or fatigue and, therefore, it may adversely affect the patient's ability to drive or use machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The assessment of adverse reactions is based on the following frequency grouping:

Common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, 1/1,000), Very rare (< 1/10,000)

Metabolism and nutrition disorders

Rare: Increased triglycerides, increased liver enzymes (ALAT, ASAT)

Psychiatric disorders

Uncommon: Depression, sleep disorders

Rare: Nightmares, hallucinations

Nervous system disorders

Common: Dizziness, headache

Eye disorders

Rare: Reduced tear flow (to be taken into consideration in patients wearing contact lenses)

Very rare: Conjunctivitis

Ear and labyrinth disorders

Rare: Hearing disorders

Cardiac disorders

Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure, bradycardia

Vascular disorders

Common: Feeling of coldness or numbness in the extremities, hypotension

Rare: syncope

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease

Rare: Allergic rhinitis

Gastrointestinal disorders

Common: Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Hepatobiliary disorders

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Rare: Hypersensitivity reactions (itching, flush, rash and angioedema)

Very rare: Hair loss. Beta-blockers can trigger psoriasis, aggravate the condition or lead to psoriasis form rash

Musculoskeletal and connective tissue disorders

Uncommon: Muscle weakness, muscle cramps

Reproductive system and breast disorders

Rare: Potency disorders

General disorders and administration site conditions

Common: Fatigue

Uncommon: Asthenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

Treatment

In general, if overdose occurs, discontinuation of BETACOR treatment and supportive and symptomatic treatment is recommended.

Gastric lavage should be performed within four hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose

The data available suggest that bisoprolol is not dialyzable to any extent.

Cases of overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly.

Gastric lavage should be performed within four hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluid replacement and administration of vasopressors. Intravenous glucagon may also be useful.

Acute worsening of heart failure: Intravenous administration of diuretics, positive inotropic medicines, as well as vasodilators.

Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta-agonist, e.g. salbutamol.

Hypoglycaemia: Intravenous administration of glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.2 Adrenolytics (sympathicolytics)

Bisoprolol is a $ß_1$-selective beta-adrenoceptor antagonist with low $ß_2$-receptor affinity. It blocks beta-adrenergic receptors in the heart and the juxtaglomerular apparatus (kidneys), thus decreasing the excitability of the heart, the cardiac output, the oxygen myocardial consumption and the release of renin from the kidneys. Another factor that may be involved in contributing to the antihypertensive action is the decrease of the tonic sympathetic outflow from the vasomotor centres in the brain.

It has no intrinsic sympathomimetic activity nor membrane-stabilising properties. It reduces blood pressure, and by blockade of the cardiac $ß_1$-receptors, reduces heart rate and depresses plasma renin levels.

5.2 Pharmacokinetic properties

Absorption

Because of its moderate hepatic metabolism, it is subject only to a very small hepatic first pass metabolism. Therefore, bisoprolol displays a high bioavailability of 90 % after an oral dose and absorption is not affected by food. Tmax varies from 1 - 4 hours.

Distribution

The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3,5 l/kg. Total clearance is approximately 15 l/h.

Biotransformation

In man, 50 % of a dose is metabolised in the liver while the other 50 % is eliminated unchanged via the kidneys. None of the metabolites have $ß_1$-receptor blocking action.

Elimination

Bisoprolol excreted predominantly via the urine as unaltered substance and metabolites. The plasma elimination half-life is 10-12 hours, resulting in a duration of action of 24 hours.
Less than 2 % of the dose is excreted in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BETACOR 5 and 10, film-coated tablet

Tablet core

Calcium hydrogen phosphate, maize starch, silica, colloidal anhydrous, cellulose, crospovidone, magnesium stearate.

Film coating

Hypromellose, macrogol, dimethicone, iron oxide, titanium dioxide.

6.2 Incompatibilities

None

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 30 °C in airtight containers and protect from light.

6.5 Nature and contents of container

Blister packs containing 30 tablets.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive, Longmeadow Business Estate South, Modderfontein 1645, South Africa

Name and address of the manufacturer

Merck Healthcare KGaA

250 Frankfurterstrasse, 64293 Darmstadt, Germany

8. REGISTRATION NUMBERS

BETACOR 5 tablets: 38/5.2/0080

BETACOR 10 tablets: 38/5.2/0081

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 April 1988

10. DATE OF REVISION OF THE TEXT

TBD