PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BILOBLOK 5 mg film-coated tablets

BILOBLOK 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BILOBLOK 5 mg: Each film-coated tablet contains 5 mg bisoprolol fumarate.

BILOBLOK 10 mg: Each film-coated tablet contains 10 mg bisoprolol fumarate.

Sugar free.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

BILOBLOK 5 mg: beige, round, biconvex, uniform film-coated tablets, with breakline on one side.

BILOBLOK 10mg: brick-colored, round, biconvex, uniform film-coated tablets, with intact edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BILOBLOK is indicated in the management of mild to moderate hypertension and angina pectoris.

4.2 Posology and method of administration

Posology

BILOBLOK 5 mg tablet should be taken once a day in the morning, either on an empty stomach or with breakfast. If necessary, the dosage can be increased to 10 mg in the morning. An increase in the dosage to 20 mg daily may sometimes be necessary.

The dose should always be selected individually, particularly according to the heart rate and the therapeutic result.

Special populations

Patients with hepatic or renal impairment

It is not necessary to adjust the dose in patients suffering from mild to moderate disturbance of the liver or renal function. In patients with severe renal impairment (creatinine clearance < 20 mL/min) and in patients with severe liver function disturbance, the daily dose of 10 mg BILOBLOK must not be exceeded.

In some of these patients, halving the dose may be necessary.

The normal dose of beta-blockers should be reduced in elderly patients.

Paediatric population

Safety and efficacy in children have not been established.

Method of administration

BILOBLOK should be taken orally. The tablets should be swallowed with liquid and should not be chewed.

4.3 Contraindications

- Hypersensitivity to bisoprolol or to any of the ingredients of BILOBLOK listed in Section 6.1.
- Particular caution should be exercised with patients suffering from the following: asthma, bronchitis or chronic respiratory diseases, second or third degree heart block and

bradycardia (less than 50 beats per minute), peripheral vascular diseases and Raynaud's phenomenon. The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

- Uncontrolled cardiac failure excluding that due to hypertrophic obstructive cardiomyopathy.
- Pregnancy or lactation.
- Patients with metabolic acidosis and sinus bradycardia.
- Safety and efficacy in children have not been established.
- Untreated phaeochromocytoma (see section 4.4).

4.4 Special warnings and precautions for use

BILOBLOK must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases).
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked.
- strict fasting.
- ongoing desensitisation therapy. Bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine (adrenaline) treatment does not always yield the expected therapeutic effect.
- first degree AV block.
- Prinzmetal's angina. Cases of coronary vasospasm have been observed. Despite its high $ß_1$-selectivity, angina attacks cannot be completely excluded when BILOBLOK is administered to patients with Prinzmetal's angina.

- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- general anaesthesia.

If BILOBLOK is to be withdrawn prior to surgery, at least 48 hours should be allowed to elapse between the last dose and anaesthesia.

If BILOBLOK treatment is to be continued during surgery, care should be taken when using anaesthetic medicines such as ether, cyclopropane and trichloroethylene. Vagal dominance, if it occurs, may be corrected with atropine (1 - 2 mg I.V.).

In the perioperative period it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or of hypertension.

A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

In patients suffering from ischaemic heart disease, treatment should not be discontinued abruptly.

Caution should be taken in prescribing BILOBLOK with Class 1 antidysrhythmic medicines such as disopyramide, myocardial depressants, and inhibitors of AV conduction such as calcium antagonists.

Use with caution in combination with verapamil in patients with impaired ventricular function. This combination should not be given to patients with conduction abnormalities. Neither medicine should be administered intravenously within 48 hours of discontinuing the other.

The intravenous administration of calcium antagonists and antidysrhythmic medicines is not recommended during BILOBLOK therapy.

Caution should be exercised 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.

BILOBLOK modifies the tachycardia of hypoglycaemia.

The dosage of BILOBLOK should be adjusted in cases of severe renal function impairment.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Since BILOBLOK is a highly selective ß-adrenoreceptor blocking medicine, it may be used with caution in chronic obstructive airway disease. However, in some asthmatic patients, an increase in airway resistance may occur. This bronchospasm can usually be reversed by commonly-used bronchodilators.

Congestive cardiac failure and marked bradycardia may occur.

BILOBLOK may mask the symptoms of hyperthyroidism.

It should be used with caution in patients with hypoglycaemia.

Special note:

Digitalisation of patients receiving long-term beta-blocker 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.

Patients with pheochromocytoma usually require treatment with an alpha-adrenergic blocker.

Adverse reactions are more common in patients with renal decompensation.

Alterations in the following serum biochemical values have been observed in patients receiving bisoprolol: Liver enzymes, lipoproteins and uric acid.

Patients with psoriasis or with a history of psoriasis should be given beta-blockers (e.g. bisoprolol) with caution.

4.5 Interactions with other medicines and other forms of interaction

It can be dangerous to administer BILOBLOK concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines.

Such medicine interactions can have life-threatening consequences. It may enhance the effects of hypoglycaemic medicines in patients with diabetes mellitus as well as the effects of myocardial depressants such as lignocaine, procainamide and quinidine. The effects may be antagonised by beta-adrenoceptor stimulating medicines (e.g. isoprenaline). The hypotensive effects may be dangerously reversed by alpha-adrenoceptor stimulants. The vasoconstrictor effects may be dangerously enhanced by alpha-adrenoceptor stimulants. The effects may be enhanced by adrenergic neurone blocking medicines such as guanethidine and reserpine. The anaesthetist should be informed of BILOBLOK therapy prior to any operation.

Combinations not recommended

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

Class-I antidysrhythmic medicines (e.g. quinidine, disopyramide, lignocaine, phenytoin, flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive medicines such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive medicines may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use 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.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic medicines: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic medicines: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Anaesthetic medicines: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also Section 4.4).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimetic medicines (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both medicines.

Sympathomimetics that activate both ß- and α-adrenoceptors (e.g. noradrenaline (norepinephrine), adrenaline (epinephrine)): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these medicines leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with non-selective ß-blockers.

Concomitant use with antihypertensive medicines as well as with other medicines 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 for hypertensive crisis.

Rifampicin: The half-life of BILOBLOK can be slightly shortened by the simultaneous administration of rifampicin. An increase in the dose is generally unnecessary.

Cimetidine: The pharmacokinetics of BILOBLOK is not significantly influenced by cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

BILOBLOK is contraindicated during pregnancy (see Section 4.3).

Administration to pregnant mothers shortly before giving birth or during labour result in the newborn infant being born hypotonic, collapsed or hypoglycaemic

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. Beta-adrenoceptor blockers such as BILOBLOK reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, $ß_1$-selective adrenoceptor blockers are preferable.

Breastfeeding

BILOBLOK is contraindicated during lactation (see Section 4.3).

It is not known whether bisoprolol is excreted in human milk.

Fertility

There is no data on adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

Due to individual variations in reactions to BILOBLOK, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medicine as well as in conjunction with alcohol.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Blood disorders.

Immune system disorders

Less frequent: Hypersensitivity reactions (itching, flush, rash).

Metabolism and nutrition disorders

Less frequent: Hypoglycaemia, metabolic disturbances, weight gain.

Psychiatric disorders

Less frequent: Depression, sleep disorders, nightmares, hallucinations, restlessness, overt psychosis.

Nervous system disorders

Frequent: Dizziness*, headache*, paraethesia.

Less frequent: Syncope.

Eye disorders

Less Frequent: Reduced tear flow (to be taken into consideration in patients wearing contact lenses), conjunctivitis, disturbances of vision.

Ear and labyrinth disorders

Less frequent: Transient hearing loss.

Cardiac disorders

Frequent: Worsening of pre-existing heart failure, bradycardia.

Less frequent: Heart block, AV-conduction disturbances.

Vascular disorders

Frequent: Feeling of coldness or numbness in the extremities, hypotension.

Less frequent: Orthostatic hypotension, paradoxical hypertension, exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to the unopposed arteriolar alpha-sympathetic activation).

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease, allergic rhinitis.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, constipation, stomatitis.

Hepatobiliary disorders

Less frequent: Hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, alopecia, perspiration, beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders

Less frequent: Muscle weakness, cramps.

Reproductive system and breast disorders

Less frequent: Erectile dysfunction.

General disorders and administration site conditions

Frequent: Asthenia, fatigue*, fluid retention.

Investigations

Less frequent: Increased triglycerides, increased liver enzymes (ALT, AST).

* These symptoms occur especially at the start of treatment. They are generally mild and mostly disappear within 1 - 2 weeks.

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Congestive cardiac failure and marked bradycardia may also manifest.

A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed.

The following may occur: exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastrointestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Adverse reactions are more common in patients with renal decompensation, and patients who receive the medicine intravenously.

Reporting of suspected adverse reactions

Reporting of 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

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals.

Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly. Repeated activated charcoal is necessary in severe overdose.

Intravenous atropine (1 – 2 mg) may be used to treat severe bradycardia . If necessary, this should be followed up by a slow intravenous infusion of 25 g isoprenaline. Intravenous cardiac pacing may be required for severe bradycardia.

Bronchospasm should be treated with IV aminophylline and heart failure with digitalis and diuretics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 5.2 Adrenolytics (sympathicolytics)

Pharmacotherapeutic group: Beta blocking medicines, selective.

ATC Code: C07AB07.

Bisoprolol is a highly $ß_1$-selective beta-adrenoceptor antagonist, with low $ß_2$-receptor affinity. It has neither intrinsic sympathomimetic activity nor membrane-stabilising properties.

It reduces blood pressure, and by blockade of the cardiac $ß_1$- receptors, it reduces cardiac action, and hence myocardial oxygen demand.

The mechanism of action of β_1-adrenergic blocking medicines in hypertension is not clear, but it is known that bisoprolol reduces the heart rate and depresses plasma renin levels.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is rapidly absorbed after oral administration in man and displays a high bioavailability of 90 % after an oral dose.

Distribution

The distribution volume is 3,5 L/kg. The plasma protein binding of bisoprolol is about 30 %.

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 found in man has $ß_1$-receptor blocking action.

Elimination

In man, the plasma elimination half-life is 10 - 12 hours resulting in duration of action of 24 hours. Because of its moderate hepatic metabolism, it is subject only to a very small hepatic first pass metabolism.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Microcrystalline cellulose, pregelatinized maize starch, croscarmellose sodium, silica, colloidal anhydrous and magnesium stearate.

Film coating: Opadry® II 24286–beige (5 mg tablet) and Opadry® II 24297-brick (10 mg tablet).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C in the original package. Protect from light.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/Aluminium foil blisters strips. The blister strips are packed in cartons containing 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

BILOBLOK 5 mg: 48/5.2/0623

BILOBLOK 10 mg: 48/5.2/0624

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2022

10. DATE OF REVISION OF THE TEXT

29 March 2022

BIL/C/PI/A