PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BISLO 5 mg film-coated tablets

BISLO 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

BISLO 10: 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.

BISLO 5: Salmon pink coloured, biconvex, round, film-coated tablet, debossed with ‘UL’ on one side and break line on the other side, with ‘5’ debossed on either side of the break line.

BISLO 10: White coloured, biconvex, round, film-coated tablet, debossed with ‘UL’ on one side and ‘10’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BISLO is indicated for the management of mild to moderate hypertension and angina pectoris.

4.2 Posology and method of administration

Adults:

5 mg to 10 mg once daily, in the morning, with or without food.

The dose must be individualised according to response and tolerance.

The maximum recommended daily dose is 20 mg.

Severe renal impairment (creatinine clearance < 30 mL/min) or severe hepatic impairment:

The normal dose should be reduced in patients suffering from renal dysfunction.

Do not exceed the daily dose of 10 mg.

Elderly:

The normal dose should be reduced in elderly patients.

BISLO should not be stopped abruptly, but terminated gradually over a period of 1 – 2 weeks.

Children:

Safety and efficacy in children have not been established.

4.3 Contraindications

- Hypersensitivity to bisoprolol or to any of the excipients (see section 6.1).
- Bronchial asthma.
- Severe chronic obstructive pulmonary disease (COPD).
- Second and third-degree heart block.
- Bradycardia (less than 50 beats per minute).
- Pregnancy and lactation (see section 4.6).
- Acute cardiac failure or during episodes of cardiac failure decompensation requiring IV inotropic therapy.
- Cardiogenic shock.
- Metabolic acidosis.
- Sick sinus syndrome.
- Symptomatic hypotension.
- Phaeochromocytoma (see section 4.4).
- Hyperthyroidism, as clinical manifestations may be masked.
- Peripheral vascular diseases and Raynaud's phenomenon (see section 4.4).

4.4 Special warnings and precautions for use

The initiation and cessation of treatment with BISLO necessitates regular monitoring.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of dysrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period.

If the decision is made to withdraw BISLO before anaesthesia, at least 48 hours should be allowed to elapse between the last dose and surgery. BISLO is to be continued, care should be taken when using anaesthetics such as ether and halogenated anaesthetics (see section 4.5). The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicines, resulting in bradydysrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. Atropine (1 – 2 mg intravenous) may be used to correct vagal dominance. Normal tachycardic responses due to hypovolaemia or blood loss of the patient may be obscured during or after surgery. Particular caution should be taken in this regard.

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 hypertension.

Take special care in patients who are strictly fasting.

Psoriasis may be aggravated by BISLO.

Desensitisation therapy: Bisoprolol, as in BISLO, may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine (adrenaline) treatment does not always have the expected effect.

The dosage of BISLO should be adjusted in severe renal impairment (see section 4.2).

Care should be taken in prescribing BISLO together with Class 1 antidysrhythmic medicines, such as disopyramide, myocardial depressants and inhibitors of atrioventricular (AV) conduction, such as calcium antagonists.

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

BISLO should be used 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 therapy with BISLO (see section 4.5).

BISLO modifies the tachycardia associated with hypoglycaemia. Particular caution should be taken in diabetes mellitus, as symptoms and signs of acute hypoglycaemia, such as tachycardia, may be masked, and the response to hypoglycaemia is diminished. It may also delay recovery of insulin-induced hypoglycaemia.

Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker (see section 4.3).

BISLO may increase the number of attacks of chest pain in Prinz metal angina. Cases of coronary vasospasm have been observed.

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 BISLO is being discontinued (see section 4.2).

Digitalisation of patients receiving long-term beta-blocker therapy, such as BISLO, 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 (see section 4.5).
Exacerbation of peripheral vascular disease or the development of Raynaud’s phenomenon may occur with the use of BISLO. Peripheral gangrene may be precipitated (see section 4.3).

Although cardio selective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, these should be avoided in patients with obstructive airway diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, BISLO may be used with caution. In patients with obstructive airway diseases, the treatment with BISLO should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

Under treatment with BISLO the symptoms of a thyrotoxicosis may be masked.

BISLO must be used with caution in first degree AV block and peripheral arterial occlusive disease (aggravation of symptoms may occur especially when starting therapy).

Paediatric population

Safety and efficacy in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

Calcium channel blockers, such as the verapamil type and to a lesser extent of the diltiazem type, should not be given with BISLO as it has a negative influence on contractility and atrioventricular (AV) conduction (see section 4.4). Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antidysrhythmic medicines (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone), as the effect on atrioventricular conduction time may be potentiated and negative inotropic effect increased.

Caution should be exercised with concomitant use with central acting hypotensives, such as clonidine, methyldopa or moxonidine. Decrease in central sympathetic tonus may lead to reduction in heart rate and cardiac output, and vasodilation. Abrupt withdrawal may increase the 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.

Concomitant use of BISLO with hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines can have life-threatening consequences, for example:

- Profound hypoglycaemia with oral hypoglycaemic medicines and insulin.
- Impairment of myocardial function with antidysrhythmic medicines, such as amiodarone, as the effect on atrio-ventricular conduction time may be potentiated (see section 4.4).

Beta-adrenoceptor stimulating medicines (such as dobutamine, dopamine or isoprenaline) may antagonise the effects of BISLO.

Alpha-adrenoceptor stimulants (such as pseudoephedrine and phenylephrine), as well as adrenergic neurone blocking medicines (such as reserpine) may lead to life-threatening vasoconstriction in combination with BISLO.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with BISLO may unmask the alpha-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 nonselective beta-blockers.

Concomitant use with parasympathomimetics may increase atrioventricular (AV) conduction and bradycardia.

BISLO and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored (see section 4.4). The concomitant use with digitalis glycosides could result in reduction of heart rate and increase of atrio-ventricular conduction time.

Topical beta-blocker eye drops may add to the systemic side effects of BISLO.

Anaesthetic medicines: Attenuation of reflex tachycardia and hypotension (see section 4.4).
Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the hypotensive effects of BISLO.
Metabolism of bisoprolol (as in BISLO) may be increased by strong enzyme inducers, such as rifampicin and barbiturates, and decreased by strong enzyme inhibitors, such as erythromycin.

An enhanced antihypertensive effect is seen when angiotensin converting enzyme (ACE) inhibitors are given with BISLO. 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

Concomitant use of BISLO with mefloquine may increase bradycardia.

Co-administration with monoamine oxidase inhibitors (except MAO-B inhibitors) can result in enhanced hypotensive effect of the beta-blockers, but also risk for hypertensive crisis.

4.6 Fertility, pregnancy and lactation

BISLO should not be taken during pregnancy or lactation.

Pregnancy

Bisoprolol, as in BISLO has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Administration of BISLO to pregnant mothers shortly before birth or during labour may result in hypotonia, bradycardia, collapse or hypoglycaemia in the newborn (see section 4.3). If treatment

with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

Breastfeeding

It is not known whether bisoprolol is excreted in human milk. Therefore, breastfeeding is not recommended during administration of BISLO.

Fertility

No data on the effects on fertility are available.

4.7 Effects on ability to drive and use machines

BISLO may cause drowsiness or sleepiness. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol. The patient should not drive or operate machinery until he/she knows the effect of BISLO.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: leukopenia, thrombocytopenia

Immune system disorders

Less frequent: hypersensitivity (allergic) reactions (pruritus, rash, angioedema)

Endocrine disorders

Frequency unknown: hypoglycaemia

Metabolism and nutrition disorders

Frequency unknown: metabolic disturbances, increased uric acid levels, hypercholesterolaemia, increased triglycerides

Psychiatric disorders

Frequent: drowsiness, sleep disorders, trouble sleeping

Less frequent: anxiety, nervousness, mental depression, nightmares, vivid dreams, hallucinations, confusion

Nervous system disorders

Frequent: headache, dizziness

Less frequent: syncope

Frequency unknown: restlessness, lassitude, paraesthesia, psychosis

Eye disorders

Less frequent: dry, sore eyes, reduced tear flow (to be considered if the patient wears contact lenses), conjunctivitis

Frequency unknown: disturbances of vision

Ear and labyrinth disorders

Frequency unknown: transient hearing loss

Cardiac disorders

Frequent: bradycardia

Less frequent: congestive heart failure, dysrhythmias, atrioventricular (AV) conduction disorders, chest pain

Frequency unknown: heart block

Vascular disorders

Frequent: feeling of numbness, coldness in extremities, hypotension

Less frequent: orthostatic hypotension, reduced peripheral circulation

Frequency unknown: paradoxical hypertension, fluid retention, exacerbation of peripheral vascular disease, development of Raynaud's phenomenon, peripheral gangrene may be precipitated

Respiratory, thoracic and mediastinal disorders

Less frequent: bronchoconstriction or bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases, rhinitis/nasal congestion

Gastrointestinal disorders

Frequent: nausea, vomiting, diarrhoea, constipation

Frequency unknown: stomatitis

Hepatobiliary disorders

Less frequent: hepatoxicity, cholestatic jaundice, hepatitis

Frequency unknown: raised liver enzymes (alanine aminotransferase [ALT)]/aspartate aminotransferase [AST])

Skin and subcutaneous tissue disorders

Less frequent: skin rash, psoriasiform eruption, alopecia, activating or worsening of psoriasis

Frequency unknown: perspiration

Musculoskeletal, connective tissue and bone disorders

Less frequent: back pain or joint pain, muscle cramps, skeletal muscle weakness

Frequency unknown: myopathy

Reproductive system and breast disorders

Frequent: decreased sexual ability, erectile dysfunction

General disorders and administration site conditions

Frequent: asthenia, fatigue, weight increase

Adverse reactions are more common in patients with renal decompensation.

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 "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

With overdose (e.g. daily dose of 15 mg instead of 7,5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2 000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual up titration.

Management

If overdose occurs, BISLO treatment should be stopped and supportive and symptomatic treatment should be provided. Cases of overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-

blockers, the following general measures should be considered when clinically warranted.

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

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer IV diuretics, inotropic medicines, vasodilating medicines.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic medicines and/or aminophylline.

Hypoglycaemia: Administer IV glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.2 Adrenolytics (sympatholytics)

Pharmacotherapeutic group: Beta blocking agents, selective

ATC code: C07AB07

Bisoprolol is a selective beta1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance

and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %.

Distribution

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

Biotransformation and elimination

Bisoprolol undergoes minimal first-pass hepatic metabolism. About 50 % of a dose is metabolised in the liver and the remainder is excreted unchanged via the kidneys. The plasma elimination half-life is approximately 10 to 12 hours and the duration of action is about 24 hours.

Linearity

The kinetics of bisoprolol are linear and independent of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Crospovidone

Dibasic calcium phosphate anhydrous

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Polyethylene glycol

Polysorbate

Pregelatinised starch

Titanium dioxide (E171).

BISLO 5: Ferric oxide red and ferric oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Transparent clear PVC/PVDC/aluminium foil blister strips containing 10 tablets each. Three (3 x 10) blister strips are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico, Ground Floor, Unit 4,

10 Church Street, Durbanville,

Cape Town

7551

8. REGISTRATION NUMBERS

BISLO 5: 45/5.2/0128

BISLO 10: 45/5.2/0129

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2023

10. DATE OF REVISION OF THE TEXT

29 November 2021

NAME AND ADDRESS OF THE MANUFACTURER:

Unichem Laboratories Limited

Unit-II, Village Bhatauli Kalan, Baddi, Dist. Solan (H.P.)

173 205, India

Namibia: NS2		
Registration numbers:	BISLO 5:	16/5.2/0154
	BISLO 10:	16/5.2/0155