

1. NAME OF THE MEDICINAL PRODUCT

Soloc 10mg tablets.
Bisoprolol 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bisoprolol as 10mg bisoprolol fumarate and refer to section 6.1 for the inactive ingredients.

3. PHARMACEUTICAL FORM

Film-coated Tablets.

Clinical Particulars

4.1. Therapeutic Indications

Management of hypertension.

Management of angina pectoris.

4.2. Posology and Method of Administration

Route of administration: Oral

Dosage: Adults: Usual dose 10mg once daily.

This dose may be decreased or increased according to the patient's blood pressure and tolerance. In some patients, 5mg per day may be adequate. Maximum recommended dose is 20mg per day. In patients with final stage impairment of renal function (creatinine clearance <20 ml/min) or liver function, the dose should not exceed 10mg per day.

There is no evidence that the dosage needs to be altered for patients on renal dialysis.

Elderly: No dosage adjustment is normally required, but 5mg per day may be adequate in some patients as for other adults.

Children: Use is not recommended
There is no paediatric experience.

4.3 Contraindications

As with other β_1 -adrenoceptor antagonists, bisoprolol should not be used in cases of:

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy.
- Cardiogenic shock
- Sinoatrial block
- Second or third degree atrio-ventricular block (without a pacemaker)
- Marked bradycardia (less than 60 beats/min)-Symptomatic bradycardia,
- Extreme hypotension (systolic blood pressure <100mmHg) - Symptomatic hypotension
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Hypersensitivity to bisoprolol or to any of the excipients
- Sick sinus syndrome
- Severe forms of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated pheochromocytoma (see section 4.4)
- Metabolic acidosis

Bisoprolol is contra-indicated in patients with hypersensitivity to bisoprolol or to any of the excipients (see section 6.1).

4.4 Special Warnings and Special Precautions for Use

Warnings

applies only to CHF:

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2)

applies to all indications:

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

Precautions

applies only to hypertension or angina pectoris:

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

applies only to CHF:

The initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the dosage and method of administration see section 4.2.

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin-dependent diabetes mellitus(type I)

- severely impaired renal function
- severely impaired liver function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

applies to all indications:

Bisoprolol must be used with caution in

- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia (e.g tachycardia, palpitations or sweating) can 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.
- Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy), such as Raynaud's phenomenon.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after a careful balancing of benefits against risks. Psoriasis may be aggravated.

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol. It may unmask myasthenia gravis.

In patients with pheochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of 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 bradyarrhythmias, attenuation of reflex tachycardia, and 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.

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 beta2-stimulants may have to be increased.

For patients with severe renal impairment and patients with severe liver function disorders please refer to section 4.2.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type or with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Drug Withdrawal

Patients receiving bisoprolol should be warned not to interrupt or discontinue therapy without consulting their physician. Abrupt withdrawal should be avoided in patients receiving bisoprolol for the treatment of hypertension. When bisoprolol is discontinued in patients with coronary disease or suspected thyrotoxicosis, the patient should be observed carefully; patients with coronary artery disease should be advised to temporarily limit their physical activity. If exacerbation of angina occurs or acute coronary insufficiency develops after bisoprolol therapy is interrupted or discontinued, treatment with the drug should be re-instituted, at least temporarily.

4.5 Interaction with Other Medications and Other Forms of Interaction

- **Combinations not recommended**

applies only to CHF:

Class-I antiarrhythmic drugs (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone):

Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

applies to all indications:

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 beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting antihypertensive drugs (e.g. methyl dopa, moxonidine, rilmenidine and clonidine) Concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

- **Combinations to be used with caution**

applies only to hypertension or angina pectoris:

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

applies to all indications:

Calcium antagonists of the dihydropyridine type (e.g. 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 antiarrhythmic drugs (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 drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs:

Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents:

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.

Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

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

Concomitant use with antihypertensive agents as well as with other drugs 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

4.6 Pregnancy and Lactation

Pregnancy:

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, β -adrenoceptor blockers 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 β -adrenoceptor blockers is necessary, β_1 -selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth

is recommended. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Lactation:

There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on Ability to Drive and Use Machines

In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to operate machinery cannot be excluded. This should be considered particularly at the start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable Effects

Very common ($\geq 10\%$), common ($\geq 1\%$ and $< 10\%$), uncommon ($\geq 0.1\%$ and $< 1\%$), rare ($\geq 0.01\%$ and $< 0.1\%$), very rare ($< 0.01\%$)

Investigations

Rare: increased liver enzymes (ALAT, ASAT)

Metabolism and nutrition disorders:

Rare: increased triglycerides

Cardiac disorders:

Very common: bradycardia (in patients with chronic heart failure)

Common: worsening of pre-existing heart failure (in patients with chronic heart failure)

Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure (in patients with hypertension or angina pectoria), bradycardia (in patients with hypertension or angina pectoria).

Nervous system disorders:

Common: dizziness*, headache*.

Rare: syncope

Eye disorders:

Rare: reduced tear flow (to be considered if the patient uses contact lenses).

Very rare: conjunctivitis.

Ear and labyrinth disorders:

Rare: hearing disorders.

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.

Skin and subcutaneous tissue disorders:

Rare: hypersensitivity reactions (itching, flush, rash).

Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders:

Uncommon: muscle weakness, muscle cramps.

Vascular disorders:

Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.

General disorders:

Common: fatigue*, asthenia (patients with chronic heart failure)

Uncommon: asthenia(in patients with hypertension or angina pectoris)

Hepatobiliary disorders:

Rare: hepatitis.

Reproductive system and breast disorders:

Rare: potency disorders.

Psychiatric disorders:

Uncommon: sleep disorders, depression

Rare: nightmares, hallucinations.

applies only to hypertension or angina pectoris:

*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1-2 weeks.

4.9 Overdose

The most common signs expected with overdosage of a β -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 interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable.

Based on the expected pharmacological actions and recommendations for other β -blockers, the following general measures should be considered when clinically warranted.

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 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 temporary pacing.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, β_2 -sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Bisoprolol is a potent β_1 -selective adrenoreceptor blocking agent without intrinsic sympathomimetic activity and relevant membrane stabilising activity.

As with other β_1 -blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity.

In patients with angina, the blockade of β_1 -receptors reduces heart action and thus reduces oxygen demand. Hence, bisoprolol is effective in eliminating or reducing the symptoms.

5.2. Pharmacokinetic Properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract.

Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The drug is cleared equally by the liver and kidney.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. About 95% of the drug substances is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

5.3. Preclinical Safety Data

No relevant further data.

PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Maize Starch
Microcrystalline Cellulose
Crospovidone
Calcium Hydrogen Phosphate
Magnesium Stearate
Colloidal Silica

Film-coating:
Hypromellose
Iron Oxide (E172)
Titanium dioxide (E171)
Macrogol
Dimeticone

6.2. Incompatibilities

None stated.

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

PVC /PVDC aluminium blister packs
Blister pack sizes 28, 30, 56, 100 & 112

Blister packs 28, 56 & 112 containing strips of 14 tablets.
Blister packs 30 & 100 containing strips of 10 tablets.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
Addiscombe Road
Croydon
CR0 0XT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 12762/0054

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