Directions for Use — Please Read Carefully!

BisoHEXAL® 2.5 mg / 5 mg — Film-Coated Tablet

CONTENT

BisoHEXAL® 2.5 mg Tab: Each film-coated tablet contains 2.5 mg bisoprolol fumarate (2:1).
BisoHEXAL® 5 mg Tab: Each film-coated tablet contains 5 mg bisoprolol fumarate (2:1).

DESCRIPTION

BisoHEXAL® 2.5 mg Tab: White coloured, round, snap tab film-coated tablets, divisible into two parts with a one-sided embossment "BIS 2.5".
BisoHEXAL® 5 mg Tab: Yellow coloured, round, snap tab film-coated tablets, divisible into four parts with a one-sided embossment "BIS 5".

INDICATIONS

- Essential hypertension
- Coronary heart disease (angina pectoris)
- Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction ≤ 35 %, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section *Pharmacodynamics*).

RECOMMENDED DOSAGE

Adults

Treatment of hypertension or angina pectoris

The recommended dosage is 5 mg bisoprolol fumarate (equivalent to 2 tablets of **BisoHEXAL® 2.5 mg Tablet** or 1 tablet of **BisoHEXAL® 5 mg Tablet**) once daily. If necessary, the dose may be increased to 10 mg bisoprolol fumarate (equivalent to 4 tablets of **BisoHEXAL® 2.5 mg Tablet** or 2 tablet of **BisoHEXAL® 5 mg Tablet**) once daily.
The maximum recommended dose is 20 mg once daily.
In all cases the dose is adjusted individually, in particular according to the pulse rate and therapeutic success. **BisoHEXAL®** must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Treatment of stable chronic heart failure

Standard treatment of chronic heart failure consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics and when appropriate cardiac glycosides. The patient should be stable (without acute failure) when **BisoHEXAL®** treatment is initiated. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Titration phase

The treatment of stable chronic heart failure with **BisoHEXAL®** requires a titration phase.
The treatment of stable chronic heart failure with **BisoHEXAL®** is initiated according to the following titration scheme, individual adaptation may be necessary depending on how well the patient tolerates each dose, i.e. the dose is to be increased only, if the previous dose is well tolerated.

1st week	: 1.25 mg once daily*
2nd week	: 2.5 mg once daily
3rd week	: 3.75 mg once daily*
4th – 7th week	: 5 mg once daily
8th – 11th week	: 7.5 mg once daily
12th week and beyond	: 10 mg once daily as maintenance treatment

* Bisoprolol 5 mg and 10 mg is not suitable for initial treatment of stable chronic heart failure. Lower strengths are available for this purpose.

The maximum recommended dose is 10 mg once daily.
Close monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating therapy.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.
In case of transient worsening of heart failure, hypotension or bradycardia, reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of **BisoHEXAL®** or to consider discontinuation.

Reconsideration and/or uptitration of **BisoHEXAL®** should always be considered when the patient becomes stable again.

Duration of treatment

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

The treatment with **BisoHEXAL®** must not be stopped abruptly or change the recommended dose without talking to your doctor first since this might lead to a transitory worsening of condition. Especially in patients with ischaemic heart disease, treatment must not be discontinues suddenly. Gradual reduction of the daily dose is recommended.

Special Populations

Renal or hepatic impairment

Treatment of hypertension or angina pectoris

In patients with liver or kidney function disorders of mild to moderate severity, no dose adjustments is normally required. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic impairment a daily dose of 10 mg bisoprolol must not be exceeded.

Treatment of stable chronic heart failure

There is no information regarding the pharmacokinetics of bisoprolol in patients with chronic heart failure and concomitant hepatic or renal impairment. Titration of the dose in these populations must therefore be made with particular caution.

Elderly

No dosage adjustment is required.

Children

There is no experience with bisoprolol in children, therefore its use is not recommended for children.

METHOD OF ADMINISTRATION

BisoHEXAL® should be taken in the morning with or without food. The tablets should be swallowed with some liquid and should not be chewed.

CONTRAINDICATIONS

Bisoprolol is contraindicated in patients with:

- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- bradycardia with less than 60 beats/min before the start of therapy
- hypotension (systolic blood pressure less than 100 mmHg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see *Warning and Precautions*)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

WARNING & PRECAUTIONS

Applies only to chronic heart failure

The treatment of stable chronic heart failure with **BisoHEXAL®** has to be initiated with a special titration phase. The initiation and cessation of treatment of stable chronic heart failure with **BisoHEXAL®** necessitates regular monitoring.

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

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Applies to all indications

Especially in patients with ischaemic heart disease the cessation of therapy with **BisoHEXAL®** must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.

Bisoprolol 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
- first degree AV block
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)

In patients undergoing general anaesthesia, the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Combination of bisoprolol with calcium antagonists of the verapamil and diltiazem type, with Class I antiarrhytmic drugs and with centrally acting antihypertensive drugs is generally not recommended. For details please refer to section *Interaction with Other Medicaments*.

In bronchial asthma or other chronic obstructive lung 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.

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.

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

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

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

The initiation of treatment with bisoprolol necessitates regular monitoring. The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information please refer to section *Recommended Dosage*.

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

Effects on Ability to Drive and Use Machines

Depending on the individual patients response to treatment, the ability to drive a vehicle or to use machines may be impaired. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

INTERACTIONS WITH OTHER MEDICAMENTS

Combinations not recommended

Applies only to chronic heart failure

- *Class I antiarrhythmic drugs (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone):* Effect on atrioventricular 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 atrioventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

- *Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine):* Concomitant use of centrally acting antihypertensive drugs 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

Applies only to hypertension or angina pectoris

- *Class-I antiarrhythmic drugs:* Effect on atrioventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications

- *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 antiarrhythmic drugs (e.g. amiodarone):* Effect on atrioventricular conduction time may be potentiated.
- *Topical beta-blockers (e.g. eye drops for glaucoma treatment):* May add to the systemic effects of bisoprolol.
- *Parasympathomimetic agents:* Concomitant use may increase atrioventricular conduction time and the risk of bradycardia.
- *Insulin and oral antidiabetic drugs:* Intensification 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 *Warning and Precautions*).
- *Digitalis glycosides:* Reduction of heart rate, increase of atrioventricular conduction time.
- *Non-steroidal anti-inflammatory drugs (NSAIDs):* NSAIDs may reduce the hypotensive effect of bisoprolol.
- *β-Sympathomimetic agents (e.g. isoprenaline, dobutamine):* Combination with bisoprolol may reduce the effect of both agents.
- *Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline):* Combination with bisoprolol may unmask the α-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 β-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 for hypertensive crisis.

PREGNANCY AND LACTATION

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-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 beta-adrenoceptor blockers is necessary, $beta_1$-selective adrenoceptor blockers are preferable.

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

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

SIDE EFFECTS

Psychiatric disorders Uncommon : Depression, sleep disorders Rare : Nightmares, hallucinations	Nervous system disorders Common: Dizziness*, headache* Rare: Syncope
Eye disorders Rare: Reduced tear flow Very rare: Conjunctivitis	Ear and labyrinth disorders Rare: Hearing disorders
Cardiac disorders Very common: Bradycardia (in patients with chronic heart failure) Common: Worsening of per-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 pectoris); bradycardia (in patients with hypertension or angina pectoris)	Vascular disorders Common: Feeling of coldness or numbness in the extremities, hypotension Uncommon: Orthostatic hypotension
Gastrointestinal disorders Common: Gastrointestinal complains such as nausea, vomiting, diarrhoea, constipation.	Respiratory, thoracic and mediastinal disorders Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease Rare: Allergic rhinitis
Skin and subcutaneous tissue disorders Rare: Hypersensitivity reactions such as itching, flush, rash Very rare: Alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.	Hepatobiliary disorders Rare: Hepatitis
Reproductive system and breast disorders Rare: Potency disorders	Musculoskeletal and connective tissue disorders Uncommon: Muscle weakness, muscle cramps
Investigations Rare: Increased triglycerides, increased liver enzymes (ALAT, ASAT)	General disorders and administration site conditions Common: Asthenia (patients with chronic heart failure), fatigue* Uncommon: Asthenia (in patients with hypertension or angina pectoris)
	* Applies only to hypertension or angina pectoris: These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

SYMPTOMS AND TREATMENT OF OVERDOSAGE & ANTIDOTE

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 overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

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 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 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 transvenous cardiac pacemaker insertion.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

PHARMACODYNAMICS

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilizing activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

Bisoprolol is used for the treatment of hypertension and angina.

In acute administration in patients with coronary heart disease without chronic heart failure, bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

PHARMACOKINETICS

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10 - 12 hours gives a 24-hour effect after once daily dosing .

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent, a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

The kinetics of bisoprolol are linear and independent of age.

PRESENTATION

Box of 30, 50 and 100 film-coated tablets

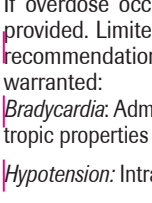
Shelf life: Please refer to the outer box label.
Store in a cool dry place, not above 30°C.

LIST OF EXCIPIENTS

Tablet core: Anhydrous calcium hydrogen phosphate, Cellulose, microcrystalline, Pregelatinised maize starch, Croscarmellose sodium, Silica colloidal anhydrous, Magnesium stearate, Lactose monohydrate.

Film coating: Opadry White, Ferric oxide yellow E172 (colorant for 5 mg).

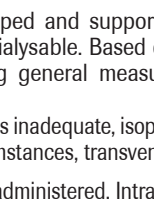
BisoHEXAL® 2.5 mg Tablet



Place the tablet on a hard, flat surface with the scored side at the top.

Press with the thumb on the middle of the tablet and the tablet will break into two halves.

BisoHEXAL® 5 mg Tablet



Place the tablet on a hard, flat surface with the scored side at the top.

Press with the thumb on the middle of the tablet and the tablet will break into two halves, press with the thumb in the middle of each half and you will have four parts.

Keep medicines out of reach of children
Jauhi daripada kanak-kanak

Manufactured for:
HEXAL AG
Holzkirchen, Germany.

By:
LEK S.A.
Stryków, Poland.

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