# APPROVED BY

Order of the Ministry

of Health of Ukraine

No. 182 dated 30.03.2015

**Marketing Authorization**

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**AMENDED**

**Order of the Ministry**

**of Health of Ukraine**

**No. 1225 of 10.11.2016**

## INSTRUCTION

## for medical use of medicinal product

### BISOPROL®

***Composition:***

*Active substance:* bisoprolol;

1 tablet contains 2.5 mg bisoprolol fumarate as calculated on 100 % substance;

*Excipients:* microcrystalline cellulose, calcium hydrogen phosphate, crospovidone, anhydrous colloidal silicon dioxide, magnesium stearate.

**Pharmaceutical form**

Tablets.

*Basic physical and chemical properties:* White, round, biconvex, scored or unscored tablets. Marbled surface of the tablet is allowed.

**Pharmacotherapeutic group**

Beta blocking agents, selective. ATC Code С07А В07.

**Pharmacological properties**

*Pharmacodynamics*

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent lacking intrinsic sympathomimetic activity and relevant membrane stabilising properties. It has antianginal and hypotensive effect. It decreases myocardial oxygen demand due to reduced heart rate and cardiac output and decreased blood pressure, and increases myocardial oxygen supply due to decreased end-diastolic pressure and lengthened diastole. 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.

The drug only in isolated cases can affect the smooth bronchial muscles and peripheral arteries, as well as glucose metabolism.

*Pharmacokinetics*

*Absorption.* Bioavailability is about 90% after oral administration and is not dependent on food intake.

*Distribution.* The volume of distribution is 3.5 L/kg. Bisoprolol is bound to plasma proteins at approx. 30%.

*Metabolism and excretion.* 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. The total bisoprolol clearance is 15 L/hr. The diuretic duration of effect is 10-12 hours depending on the dose, the antihypertensive effect is maintained up to 24 hours.

*Linearity.* The kinetics of bisoprolol is linear and independent of age.

*Special populations.* Since 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. In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

**Clinical particulars**

***Indications***

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

***Contraindications***

*–* acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy;

*–* cardiogenic shock;

*–* second or third degree AV block;

*–* sick sinus syndrome;

*–* sinoatrial block;

*–* symptomatic bradycardia;

*–* symptomatic hypotension;

*–* severe bronchial asthma or severe chronic obstructive pulmonary disease;

*–* severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome;

*–* untreated phaeochromocytoma;

*–* metabolic acidosis;

*–* hypersensitivity to the active substance or to any of the excipients.

***Interactions with other medicinal products and other forms of interaction***

*Combinations not recommended*

* 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.
* 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 beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.
* Centrally-acting antihypertensive drugs (e.g. clonidine methyldopa, moxonidine, rilmenidine): 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 the risk of "rebound hypertension".

*Combinations to be used with caution:*

* Calcium antagonists of the dihydropyridine type (e.g. nifedipine, felodipine and amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the negative effect on the inotropic function of the myocardium 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.
* Cardiac glycosides: Increase of atrio-ventricular conduction time, reduction in heart rate.
* Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
* Beta-sympathomimetics (e.g. isoprenaline, dobutamine): Combination with Bisoprolol® may reduce the effect of both agents.
* Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. epinephrine, norepinephrine): 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.

***Special warnings and precautions for use***

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase.

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. The initiation and cessation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring.

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions: type I diabetes mellitus, severely impaired renal function, severely impaired liver function, restrictive cardiomyopathy, congenital heart disease, haemodynamically significant organic valvular disease, myocardial infarction within 3 months.

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 (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. Aggravation of symptoms may occur especially when starting therapy;
* general anaesthesia.

In patients undergoing general anaesthesia the anaesthetist must be aware of beta-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 the 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.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended (see Section “Interactions with other medicinal products and other forms of interaction”).

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.

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.

In patients with phaeochromocytoma Bisoprolol® must not be administered until after alpha-receptor blockade. The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

The cessation of therapy with Bisoprolol® should not be done abruptly unless clearly indicated.

***Use during 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, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment 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 consideration of alternative treatment is recommended.

The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

*Lactation.*

There is 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.

***Effects on ability to drive and use machines***

In a study with coronary heart disease patients, bisoprolol did not impair driving performance.

However, 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.

***Posology and method of administration***

Tablets should be taken in the morning before or during breakfast without chewing with a little water.

Standard treatment of chronic heart failure: ACE inhibitors or angiotensin II receptor blocker, beta-blocking agents, diuretics, and when appropriate cardiac glycosides.

Patients should be stable when bisoprolol treatment is initiated. Transient worsening of heart failure hypotension or bradycardia may occur during the titration period and thereafter.

*Titration phase.*

The treatment of chronic heart failure with Bisoprolol® is to be started with the titration scheme given below and can be adjusted individually (see Table 1).

*–* 1.25 mg\* of bisoprolol fumarate once daily for 1 week, if well tolerated increase to

– 2.5 mg of bisoprolol fumarate once daily for a further week, if well tolerated increase to

– 3.75 mg\* of bisoprolol fumarate once daily for a further week, if well tolerated increase to

– 5 mg of bisoprolol fumarate once daily for the 4 following weeks, if well tolerated increase to

*–* 7.5 mg\* of bisoprolol fumarate once daily for the 4 following weeks, if well tolerated increase to

– 10 mg of bisoprolol fumarate once daily for the maintenance therapy.

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| **Titration weeks** | **Titration dose (mg)** |
| Week 1 | 1.25\* |
| Week 2 | 2.5  |
| Week 3 | 3.75\*  |
| Week 4 | 5  |
| Week 5 | 5  |
| Week 6 | 5  |
| Week 7 | 5  |
| Week 8 | 7.5\*  |
| Week 9 | 7.5\*  |
| Week 10 | 7.5\*  |
| Week 11 | 7.5\*  |
| Week 12 | 10  |

\*Use bisoprolol products with the possibility of such dosing.

The maximum recommended dose of bisoprolol fumarate is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure) 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 bisoprolol or to consider discontinuation. The reintroduction of bisoprolol should always be considered when the patient becomes stable again.

Treatment with Bisoprolol® is long-term.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal without doctor’s advice may lead to acute deterioration of the patient's condition. If necessary, treatment should be withdrawn slowly, gradually reducing the dose.

*Renal or liver impairment.*

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

When prescribing the drug to *the elderly patients* dosage correction is not required.

***Paediatric population***

There is no clinical data on the efficacy and safety of bisoprolol in children, therefore its use cannot be recommended for children.

***Overdose***

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-blocking agent are bradycardia, hypotension, acute cardiac insufficiency, hypoglycaemia and bronchospasm. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients showing bradycardia 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 uptitration (see section “Posology and method of administration”).

In case of overdose get immediate medical help.

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-blocking agents, the following general measures should be considered when clinically warranted.

Bradycardia: Atropine should be administered intravenously. 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 intravenous diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Bronchodilator therapy such as isoprenaline, beta2-sympathomimetic medicinal products and/or aminophylline should be administered.

Hypoglycaemia: Intravenous glucose should be administered.

***Undesirable effects***

*Cardiac and vascular disorders:* bradycardia, worsening of heart failure, feeling of coldness or numbness in the extremities, essential hypotension, disturbance of AV conduction, orthostatic hypotension.

*Nervous system disorders:* dizziness, headache, loss of consciousness.

*Eye disorders:* reduced tear flow (to be taken into account if the patient uses contact lenses), conjunctivitis.

*Ear disorders:* hearing disorders.

*Respiratory system disorders:* bronchospasm in patients with bronchial asthma or history of chronic obstructive pulmonary disease; allergic rhinitis.

*Gastrointestinal disorders:* nausea, vomiting, diarrhoea, constipation.

*Skin and subcutaneous tissue disorders:* hypersensitivity reactions such as pruritus, flush, rash, alopecia. Beta-blockers can worsen psoriasis or induce a psoriasis-like rash.

*Musculoskeletal disorders:* muscular weakness and cramps.

*Hepatic disorders:* hepatitis.

*Reproductive system disorders:* impotence.

*Psychiatric disorders:* depression, sleep disorders, nightmares, hallucinations.

*Laboratory tests:* increased blood triglycerides, increase in liver enzymes (ASAT, ALAT).

*General disorders:* asthenia, fatigue.

*If adverse or undesirable effects occur, the doctor should be informed immediately.*

***Shelf-life***

2 years.

Do not use after expiry date stated on the carton.

**Storage**

Store in the original package below 25 °C.

Keep out of reach of children.

Nature and contents of container

10 tablets in a blister 2, 3 or 5 blisters per carton.

Prescription status

Prescription only.

**Manufacturer**

JSC Farmak.

**Location**

74, Frunze str., Kyiv, Ukraine, 04080

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10.11.2016.