Betapro®

Bisoprolol Fumarate
2.5 mg, 5 mg and 10 mg Tablet

Description

Betapro® is a preparation of Bisoprolol Fumarate. Bisoprolol is used alone or in combination with other medications to treat high blood pressure. Bisoprolol is in a class of medications called beta blockers. It works by relaxing blood vessels and slowing heart rate to improve and decrease blood pressure.

Mode of Action

Bisoprolol Fumarate is a synthetic, beta1-selective (cardioselective) adrenoceptor blocking agent, lacking intrinsic sympathomimetic 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 beta1-selectivity extends beyond the therapeutic dose range.

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

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.

Indications

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

Dosage and Administration

Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Usual Adult Dose

Hypertension and Angina:

5–10 mg once daily; maximum 20 mg per day

Adjunct in heart failure:

Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

1.25 mg once daily for 1 week, if well tolerated increase to

2.5 mg once daily for a further week, if well tolerated increase to

3.75 mg once daily for a further week, if well tolerated increase to

5 mg once daily for the 4 following weeks, if well tolerated increase to

7.5 mg once daily for the 4 following weeks, if well tolerated increase to

10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

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 the 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 and/or uptitration of bisoprolol 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 bisoprolol must not be stopped abruptly since this might lead to a transitory worsening of condition. Especially in patients with ischemic heart disease, treatment must not be discontinued suddenly. Gradual reduction of the daily dose is recommended.

Pediatric Use

There is no experience with bisoprolol in children and adolescents, therefore its use cannot be recommended for children.

Elderly

No dosage adjustment is required.

Renal impairment

Reduce dose if eGFR less than 20 mL/minute/1.73 m^2 (max. 10 mg daily).

Hepatic impairment

Maximum 10 mg daily in severe impairment.

Contraindications

Bisoprolol Fumarate is contraindicated in chronic heart failure patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Acute heart failure or during episodes of heart failure decomposition requiring i.v. inotropic therapy
- Cardiogenic shock
- Second or third degree AV block (without a pacemaker)
- Sick sinus syndrome
- Sino-Atrial block
- Bradycardia with less than 60 beats/min before the start of therapy
- Hypotension (systolic blood pressure less than 100 mm Hg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome

- Untreated pheochromocytoma
- metabolic acidosis

Special Warnings and Precautions

Bisoprolol Fumarate must be used with caution in:

• Bronchospasm (bronchial asthma, obstructive airways diseases)

• Diabetes Mellitus with large fluctuations in blood glucose values; symptoms of hypoglycemia can be masked

• Strict fasting

• Ongoing desensitization therapy

• First degree AV block

• Prinzmetal's angina

• Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)

• General anesthesia

Drug Interactions

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

Centrally-acting antihypertensive medicinal products such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally-acting antihypertensive medicinal products 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-blocking agent discontinuation, 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.

Class-III antiarrhythmic medicinal product (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

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

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

Insulin and oral antidiabetic medicinal products: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycemia.

Anesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

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.

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 medicinal products 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-blocking agents but also risk for hypertensive crisis.

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug metabolizing enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Use in pregnancy and lactation

Pregnancy

Pregnancy Category C

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labor. Adverse effects (e.g. hypoglycemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blocking agents is necessary, beta1-selective adrenoceptor blocking agents are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the fetal growth is recommended. In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycemia and bradycardia are generally to be expected within the first 3 days.

Lactation

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

Side Effects

Uncommon

Cramp, depression, muscle weakness.

Rare

Hearing impairment, hypertriglyceridemia, syncope

Very rare

Conjunctivitis.

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 β-blocking agent are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycemia.

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 pharmacologic actions and recommendations for other beta-blocking agents, 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 IV diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta 2-sympathomimetic medicinal products and/or aminophylline.

Hypoglycaemia: Administer IV glucose.

Pharmaceutical Precautions

Keep out of the reach of children. Keep in a cool & dry place. Protect from light and moisture.

Commercial Pack

Betapro® 2.5 Tablet: Box containing 30 tablets in 3X10's blister strips. Each film coated tablet contains Bisoprolol Fumarate USP 2.5 mg.

Betapro® 5 Tablet: Box containing 30 tablets in 3X10's blister strips. Each film coated tablet contains Bisoprolol Fumarate USP 5 mg.

Betapro® 10 Tablet: Box containing 30 tablets in 3X10's blister strips. Each film coated tablet contains Bisoprolol Fumarate USP 10 mg.

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Manufactured by

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