This medicine contains two medicinal ingredients: **Bisoprolol** and Aspirin (**acetylsalicylic acid**).

**This medicine is used for**

- The treatment of hypertension in a patient whose condition is stabilized prior to individual components.
- The treatment of angina pectoris in patients whose condition is stabilized prior to individual components.

**Dosage and administration**

**Special populations**

Elderly: Usually, it is not necessary to dose adjustment, however, a dose of 5 mg bisoprolol daily at some patients may be appropriate. Renal or hepatic impairment: Since it contains acetylsalicylic acid, a medicine cannot be used in patients with severe renal or hepatic impairment. Caution is needed in patients with mild or moderate renal or hepatic impairment. Children: The safety and effectiveness of bisoprolol in children and adolescents is not determined. Thus, the capsules containing bisoprolol and acetylsalicylic acid should not be used to children and adolescents.
**Duration of treatment**

Bisoprolol treatment is usually prolonged. Bisoprolol treatment should not be stopped abruptly as this may cause a transient worsening of patients. This is particularly important in patients with ischemic heart disease. It is recommended to gradually reduce the dose.

**Contraindications**

Do not use this medicine if you are:

- Hypersensitivity to bisoprolol.
- Hypersensitive to derivatives of salicylic acid or a prostaglandin synthase inhibitors (e.g., *patients with asthma in which can lead to asthma seizures or unconsciousness*).
- Hypersensitive to any of the excipients.
- Acute heart failure or during episodes of heart failure requiring iv inotropic therapy.
- Cardiogenic shock.
- AV block second or third degree (*without pacemaker*).
- Significant bradycardia (*less than 60 heart beats per minute before treatment*
- Hypotension (*systolic blood pressure < 100 mmHg*).
- Severe bronchial asthma or severe chronic obstructive pulmonary disease.
- Suffering from a severe form of peripheral arterial occlusive disease, or Raynaud's syndrome.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Abdominal pain, or in patients who while prior treatment for the medicine had stomach pain.
- Active peptic ulcer and/or gastric/intestinal bleeding.
- Hemorrhagic cerebrovascular event in the history.
- Severe renal or hepatic failure.
- Hemorrhagic diathesis or coagulation disorders such as hemophilia and hypoprothrombinemia.
- Lack of glucose-6-phosphate dehydrogenase (*G6PD deficiency*).
- Treated with methotrexate at a dose of 15 mg per week.
- Hypersensitive to peanut or soya.

**Warnings and precautions**

**Bisoprolol**

Bisoprolol must be administered with caution to patients:

- Having diabetes with large fluctuations in the level of blood glucose; symptoms of hypoglycemia (e.g., *tachycardia, palpitations, sweating*) can be disguised.
- For strict fasting.
- As with other beta - blockers, bisoprolol may increase sensitivity to allergens and the severity of anaphylactic reactions. Administration of epinephrine does not always result in the expected therapeutic effect.
- Having AV block (*first degree*).
- Suffering from Prinzmetal angina.
- Having peripheral arterial occlusive disease. May lead to deterioration of symptoms, particularly to the beginning of treatment.
Bisoprolol should be used with caution in patients with hypertension or angina pectoris associated with heart failure. In patients with psoriasis or in those who have suffered from psoriasis, beta-blockers (e.g., bisoprolol) may be prescribed only after a careful assessment of benefit to risk. Bisoprolol treatment can mask symptoms of thyrotoxicosis. In patients with phaeochromocytoma bisoprolol can be applied only after the alpha-receptor blockade. The patient under general anesthesia, beta-blockers decrease the incidence of myocardial ischemia and arrhythmias during induction of anesthesia and post-operative intubation period. Currently it is recommended continuation of the beta-blockers during the perioperative period. The anesthesiologist needs to know that the patient is taking beta-blockers because of possible interactions with other medicines, that may result bradyarrhythmia, weakening of the reflex tachycardia and reduced reflex ability to compensate the loss of blood. If it is considered that treatment with beta-blockers must terminate before the surgery, the dose should be gradually decrease, so that the treatment with beta-blockers is completed approximately 48 hours prior to anesthesia. In bronchial asthma and other chronic obstructive pulmonary diseases which may cause the similar symptoms, it is recommended to simultaneously treat with bronchodilators. Occasionally, in patients with asthma may occur an increase in airway resistance which require increasing the dose of beta 2-agonists. The combination of bisoprolol with calcium channel blockers (diltiazem and verapamil) or with centrally acting antihypertensives are usually not recommended. As with other beta-blockers, bisoprolol can increase the susceptibility to and severity of anaphylactic allergen reaction. Administration of epinephrine does not always produce the expected therapeutic effect.

**Acetylsalicylic acid (Aspirin)**

Concomitant use with anticoagulants (coumarin derivatives, heparin) is not recommended and generally should be avoided. If concomitant use can not be avoided, it is necessary to frequently monitor international normalized ratio (INR), and patients should be advised to watch for signs of bleeding, particularly in gastrointestinal tract. Careful monitoring is also necessary for patients with bronchial asthma, allergic rhinitis (acetylsalicylic acid can cause severe urticaria, angioedema, or bronchospasm). Patients with a history of peptic ulcer and/or bleeding in the digestive system should avoid applying acetylsalicylic acid (which can cause irritation of the mucosa of the digestive system and bleeding). If signs and symptoms of bleeding caused by acetylsalicylic acid persist, the doctor may stop treatment with this medicine. Caution is required in patients with hepatic failure (since the acetylsalicylic acid generally is metabolized in the liver) and in patients with renal failure. Co-administration of these active ingredients with medicines like benzbromarone, probenecid, sulfinpyrazone is not recommended. Acetylsalicylic acid should be used with caution in cases of very severe menstrual bleeding. It is desirable to terminate the application of acetylsalicylic acid prior to the surgical procedure (including the extraction of tooth) because of the risk of a prolonged bleeding time or a bleeding deterioration. The length of treatment discontinuation must determine on a case-by-case basis, but typically lasts one week. This medicine usually contains soy lecithin and should not be taken for patients allergic to soy or peanuts.

**Athletes**

Athletes should be aware that this medicine contains the active substance that can cause a positive reaction to the medicine test.
Interactions (Use with other medicines)

Bisoprolol

- Calcium channel blockers of the verapamil type and to a lesser extent diltiazem type: negative effect on atrioventricular conduction and contractility. Intravenous administration of verapamil in patients receiving beta-blockers can cause pronounced hypotension and atroventricular block.
- Centrally acting antihypertensives (e.g., clonidine, methyldopa, moxonidine, rilmenidine): Concomitant application of centrally acting antihypertensive agent may lead to a further reduction of the central sympathetic tone, thus slowing the heart rate, and the reduction of cardiac ejection vasodilatation.

Abrupt discontinuation of antihypertensive agents that act centrally, especially before discontinuation beta-blockers may increase the risk of return ("rebound") hypertension.

Combinations that requiring caution when applying

- Class I antiarrhythmic medicines (e.g., quinidine, disopyramide, lidocaine, phenytoin, flecaainide, propafenone) may be potentiated the effect of the atrioventricular conduction time and increased negative inotropic effect.
- Dihydropyridine calcium channel blockers such as amlodipine and felodipine: Concomitant administration can increase the risk of hypotension and the risk of further deterioration of the ventricular work stations in patients with heart failure.
- Class III antiarrhythmics (e.g., amiodarone) may be potentiated the effect of atrioventricular conduction time.
- Parasympathomimetics: concomitant use may increase the atrioventricular conduction time and increase the risk of bradycardia.
- Topical application of the beta-blockers (e.g., eye drops for the treatment of glaucoma) may contribute to the system effect of bisoprolol.
- Insulin and oral antidiabetic medicines: increased effect of lowering blood sugar levels. Blockade of the beta receptors may mask the symptoms of hypoglycemia.
- Anesthetics:
  - The weakening of the reflex tachycardia and increase the risk of hypotension.
- Digitalis glycosides (digoxin): Slowing of the heart rate, lengthening the time of atrioventricular conduction.
- Nonsteroidal anti-inflammatory medicines (NSAIDs) may reduce the hypotensive effect of bisoprolol.
- Beta-sympathomimetics (e.g., isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both medicines.
- Sympathomimetics which activate the beta-and alpha-adrenoceptors (for example, norepinephrine, epinephrine): a combination with bisoprolol may highlight their vasoconstrictor effect mediated by alpha-adrenoceptor and lead to increases in blood pressure and worsening of intermittent claudication. It is believed that these interactions are more likely with the application of non-selective beta-blocker.
- Concomitant use with antihypertensive agents as well as with other medicines that can lower blood pressure (e.g., tricyclic anti-depressants, barbiturates, phenothiazines) may increase the risk of hypotension.
Combinations to be considered

- Mefloquine
  - increased risk of bradycardia.
- Monoamine oxidase inhibitors (except the inhibitors of MAO-B)
  - increased hypotensive effect of beta-blockers, but also the risk of hypertensive crisis.
- Rifampicin
  - a slight reduction in the half-life of bisoprolol, likely due to induction of liver enzymes, which involved in the metabolizing of a medicines. Adjusting the dose of bisoprolol is not usually needed.
- Ergotamine derivatives
  - worsening of peripheral circulatory disturbances.

Acetylsalicylic acid

The application of a number of inhibitors of platelet aggregation, ie. acetylsalicylic acid, nonsteroidal anti-inflammatory medicines (NSAIDs), ticlopidine, clopidogrel, eptifibatide, increases the risk of bleeding, as well as a combination of heparin and its derivates (hirudin, fondaparinux), oral anticoagulants and thrombolytics. It should be regularly monitored for clinical and biological parameters of hemostasis.

Combinations that are contraindicated

Methotrexate (at doses 15 mg/week): the combination of methotrexate and acetylsalicylic acid increases hematologic toxicity of methotrexate because acetylsalicylic acid reduces the renal clearance of methotrexate.

Therefore, the concomitant use of methotrexate with this medicine is contraindicated.

Combinations that are not recommended

Uricosurics (benzbromarone, probenecid and sulfinpyrazone) reduces the excretion of uric acid due to competition at the level of the renal tubular secretion of uric acid. Therefore, the concomitant use of this medicine with uricosurics is not recommended.

Pregnancy and lactation

This medicine should not be used during pregnancy unless it is necessary.

Pregnancy

There are no data on the use of this medicine in pregnant women. Bisoprolol has pharmacological effects that may affect the pregnancy and/or the fetus/newborn. Generally, beta - blockers decrease the perfusion of the placenta which is associated with growth retardation of fetus, intrauterine death, abortion or premature contractions. In the fetus and newborn may occur side effects (eg. hypoglycaemia and bradycardia). If the treatment with beta-blocker is necessary, preference is provides selective beta1-adrenergic receptor blockers. Bisoprolol should not be used during pregnancy unless it is necessary. If treatment with bisoprolol is considered necessary, should be monitored utero-placental blood flow and fetal growth. In the case of adverse effects on
pregnancy or the fetus, it is necessary to consider alternative therapeutic measures. Newborn child should be closely monitored. Symptoms of hypoglycaemia and bradycardia are usually expected within the first 3 days of life. Effects of acetylsalicylic acids may involve inhibition of contractions, early \textit{(intrauterine)} closing ductus arteriosus, pulmonary hypertension of the newborn and failure tricuspid valve; kidney damage with possible renal failure and oligohydramnios and blood clotting.

Breastfeeding

It is not known whether bisoprolol is excreted in human milk. Salicylic acid and its metabolites in the small amounts are excreted in breast milk. Therefore, breast-feeding is not recommended during administration of this medicine. No information about the possible effects of this medicine on fertility in women or in men.

Side effects

Bisoprolol

- Cardiac disorders
  - Very common: bradycardia
  - Common: worsening of existing heart failure
  - Uncommon: disorders in AV conducting
- Ear and labyrinth disorders
  - Rare: hearing loss
- Eye disorders
  - Rare: decreased tear secretion \textit{(especially if the patient wears contact lens)}
  - Very rare: conjunctivitis
- Gastrointestinal disorders
  - Common: nausea, vomiting, diarrhea, constipation
- General disorders and administration site conditions
  - Frequent: asthenia, fatigue
  - Uncommon: muscle weakness and cramps
- Hepatobiliary disorders
  - Rare: elevated liver enzymes \textit{(ALT, AST)}, hepatitis
- Metabolism and nutrition disorders
  - Rare: elevated triglyceride levels
- Nervous system disorders
  - Common: fatigue, dizziness, headache
  - Uncommon: sleep disturbances, depression
  - Rare: nightmares, hallucinations, syncope
- Reproductive system
  - Rare: disturbances of potency
- Respiratory, thoracic and mediastinal disorders
  - Uncommon: bronchospasm in patients with bronchial asthma or obstructive pulmonary disease in history.
  - Rare: allergic rhinitis
- Skin and subcutaneous tissue disorders
  - Rare: hypersensitivity reactions \textit{(itching, redness, feeling the heat, rash)}
  - Very rare: alopecia \textit{(loss of hair)}; beta-blockers can induce the formation of psoriasis
symptoms worse or cause rash similar to psoriasis

- Vascular disorders
  - Common: feeling of coldness and numbness of the limbs
  - Uncommon: orthostatic hypotension

These symptoms occur in particular at the start of treatment. They are usually mild and disappear within 1-2 weeks.