BELANJ

INSTRUCTIONS FOR THE MEDICINAL PRODUCT

Trade name: Belanj.
International nonproprietary name: Bisoprolol.
Dosage form: Film coated tablet.
Composition: Each film coated tablet contains:
Active substance:
Bisoprolol fumarate 5 mg.
Excipients: starch pregelatinized, cellulose microcrystalline, crosspovidone, silica colloidal anhydrous, magnesium stearate, hypromellose, macrogol 6000, talc, titanium dioxide, color iron oxide yellow (E172).
Pharmacotherapeutic group: Beta blocking agents, selective.
ATCClassification: C07AB07.
Pharmacologic property:
Pharmacodynamics:
Bisoprolol is a potent highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and without relevant membrane stabilising activity. 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. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.
Hypertension or angina pectoris:
Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta- 1-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.
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.
Pharmacokinetics:
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 plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.
The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.
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 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.
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.
Indications:

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

Contraindications:
Belanj is contraindicated in chronic heart failure patients with:

- Hypersensitivity to bisoprolol or to any of the excipients;
- Acute heart failure or during episodes of heart failure decompensation requiring IV inotropic therapy;
- Cardiogenic shock;
- Second or third degree AV block (without a pacemaker);
- Sick sinus syndrome;
- Sinoatrial block;
- Symptomatic bradycardia;
- Symptomatic hypotension;
- Severe bronchial asthma or severe chronic obstructive pulmonary disease;
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome;
- Untreated phaeochromocytoma;
- Metabolic acidosis;
- Children (there is no experience in children, therefore its use cannot be recommended for children).

Precautions: should be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.
Pregnancy and Nursing Mother:
Belanj is not recommended during pregnancy unless clearly necessary. If treatment with Belanj is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be reccomended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
There are no data on the excretion of bisoprolol excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

Dosage and directions for use:

For oral use.

Belanj tablet should be taken in morning and can be taken with food in morning. They should be swallowed in liquid and should not be chewed.

Treatment of hypertension and chronic stable angina pectoris:

Adults - the dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with renal impairment:

In *patients with severe renal impairment (creatinine clearance < 20 ml/min)* the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Patients with severe liver impairment:

No dosage adjustment is required, however careful monitoring is advised.

Elderly - no dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Discontinuation of treatment:

Treatment should not be stopped abruptly. The dosage should be diminished slowly by a weekly halving of the dose.

Treatment of stable chronic heart failure:

Adults - standard treatment of CHF 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. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

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

Titration phase:

The treatment of stable chronic heart failure with Belanj requires a titration phase.

The treatment with Belanj is to be started with a gradual uptitration according to the following steps:

- 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.

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 Belanj or to consider discontinuation.

The reintroduction and/or uptitration of Belanj should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

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

Renal or hepatic impairment:

There is no information regarding pharmacokinetics of Belanj 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.

Elderly - no dosage adjustment is normally required.

Side-effects:

The following definitions apply to the frequency terminology used hereafter:

Very common (1/10), Common (1/100, < 1/10), Uncommon (1/1,000, < 1/100), Rare (1/10,000, < 1/1,000), Very rare (< 1/10,000).

Psychiatric disorders: uncommon: sleep disorders, depression; rare: nightmares, hallucinations.

Nervous system disorders: common: dizziness, headache; rare: syncope.

Eye disorders: rare: reduced tear flow (to be considered if the patient uses lenses); very rare: conjunctivitis.

Ear and labyrinth disorders: rare: hearing disorders.

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 pectoris); bradycardia (in patients with hypertension or angina pectoris).

Vascular disorders: common: feeling of coldness or numbness in the extremities, hypotension especially in patient with heart failure.

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.

Hepatobiliary disorders: rare: hepatitis.

Skin and subcutaneous tissue disorders: rare: hypersensitivity reactions (such as itching, flush, rash); very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders: uncommon: muscular weakness and cramps.

Reproductive system and breast disorders: rare: potency disorders.

General disorders: common: asthenia (in 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.

Overdose:

The most common signs expected with overdose of a beta-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 inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of Belanj treatment and supportive and symptomatic treatment is recommended.

Drug interactive:

Combinations to be used with caution:

Applies only to hypertension or angina pectoris:

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 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 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.

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.

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.

Cautions:

Belanj must be used with caution in:

- Bronchospasm (bronchial asthma, obstructive airways diseases).

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy is recommended to 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.

- 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. Adrenaline treatment does not always give 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).
- General anaesthesia.

Effects on ability to drive and use machines:

Due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

Presentation:

Box of 30 film coated tablets of 5 mg (3 blisters x 10 tablets) with instruction for use.

Storage:

Keep in dry place, protected from light at a temperature below 25°C.

Keep out of reach of children!

Shelf life:

Labeled. Do not use after expiry date.

Distribution Condition:

Prescribed medicine.

BELINDA

The Holder of Trade Mark and Marketing Authorization is:
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