

UHS PACKAGES

120x240mm

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Cuziper™ (Bisoprolol Fumarate USP)



COMPOSITION

Cuziper 2.5mg Tablet:

Each film-coated tablet contains:
Bisoprolol Fumarate 2.5mg
USP Specs

Cuziper 5mg Tablet:

Each film-coated tablet contains:
Bisoprolol Fumarate 5mg
USP Specs

Cuziper 10mg Tablet:

Each film-coated tablet contains:
Bisoprolol Fumarate 10mg
USP Specs

DESCRIPTION

Bisoprolol fumarate is a synthetic, beta1-selective (cardioselective) adrenoceptor blocking agent.

MECHANISM OF ACTION

The mechanism of action of its antihypertensive effects has not been completely established.

Factors which may be involved include:

- Antagonism of β -adrenoceptors to decreased cardiac output.
- Inhibition of renin release by the kidneys.
- Diminution of tonic sympathetic outflow from the vasomotor centres in the brain.

PHARMACOKINETICS

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first pass metabolism resulting in an oral bioavailability of about 90 percent. Peak plasma concentrations occur 2 to 4 hours after oral doses. Bisoprolol is about 30% bound to plasma proteins. It has plasma elimination half-life of 10 to 12 hours. Bisoprolol is moderately lipid soluble. It is metabolized in the liver and excreted in urine, about 50% as unchanged drug and 50% as metabolites.

INDICATIONS AND USAGE

Bisoprolol is for oral use and meant for the following conditions:

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

DOSE AND ADMINISTRATION

Bisoprolol fumarate tablet should be taken in morning, swallowed with liquid and not to be chewed. It may be taken with food in morning.

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.

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.

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

Titration phase: The treatment of stable chronic heart failure with bisoprolol requires a titration phase. It is to be started with a gradual up-titration 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 bisoprolol or to consider discontinuation. The reintroduction and/or up-titration of bisoprolol 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 patients condition.

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

Special population

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

Elderly: No dosage adjustment is normally required.

Paediatric population: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

CONTRAINDICATIONS

Bisoprolol is contraindicated in patients with:

- 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, 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.

ADVERSE REACTIONS

The reported adverse events are sleep disorders, depression, nightmares, hallucinations, dizziness, headache, syncope, reduced tear flow (to be considered if the patient uses lenses), conjunctivitis, hearing disorders, bradycardia (in patients with chronic heart failure), worsening of pre-existing heart failure (in patients with chronic heart failure), AV-conduction disturbances, worsening of pre-existing heart failure (in patients with hypertension or angina pectoris), bradycardia (in patients with hypertension or angina pectoris), feeling of coldness or numbness in the extremities, hypotension especially in patient with heart failure, orthostatic hypotension, bronchospasm in patients with bronchial asthma or a history of obstructive airways disease, allergic rhinitis, gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation, hepatitis, hypersensitivity reactions (pruritus, flush, rash and angioedema), beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia, muscular weakness, cramps, erectile dysfunction, asthma, fatigue, increased triglycerides and increased liver enzymes.

DRUG INTERACTIONS

Combinations not recommended:

Applies only to chronic heart failure:
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 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.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyl dopa, moxonidine, rimelidine): 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 (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-adrenoceptors 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.

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.

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

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

WARNINGS AND PRECAUTIONS

Special warnings:

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

Applies to all indications:

Especially in patients with ischemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transition worsening of heart condition.

Precautions:

Applies only to hypertension or angina pectoris:
Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Applies only to chronic heart failure:

The initiation of treatment with bisoprolol 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
- restitutive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Applies to all indications:

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 does not always give the expected therapeutic effect.

- first degree AV block
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Despite its high beta1- selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- general anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidences of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance 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 the 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.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). 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 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 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.

Breastfeeding

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

OVERDOSAGE

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. The most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. Cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/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 up-titration.

DOSE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Cuziper 2.5mg Tablets: Alu-Pvc Blister Pack of 1 x 14's.
Cuziper 5mg Tablets: Alu-Pvc Blister Pack of 2 x 10's.
Cuziper 10mg Tablets: Alu-Pvc Blister Pack of 2 x 10's.

کیوزیپر
TM

(بائیسوپرولول فیوماریٹ یو ایس پی)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخے کے مطابق ہی دوا فروخت اور استعمال کی جائے۔

بچوں کی تیخنی سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔

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L1-0084-0082