FOR THE USE OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY ONLY

BISOTAB* 2.5 / 5

(Bisoprolol Fumarate Tablets USP)

GENERIC NAME

Bisoprolol Fumarate Tablets USP 2.5mg / 5mg

COMPOSITION

Each film coated tablet contains:

Bisoprolol Fumarate IP ……2.5 mg / 5mg

Colour: Red Oxide of Iron & Titanium Dioxide IP

DOSAGE FORM/S

Film coated tablets

INDICATIONS

For treatment of

- Hypertension
- Coronary heart disease (Angina pectoris)
- Congestive heart failure (CHF)

DOSE AND METHOD OF ADMINISTRATION

T*reatment 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.

Children

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

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-blocking agent, 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 bisoprolol requires a titration phase

The treatment with bisoprolol 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 uptitration 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:

Hepatic or renal impairment

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

Elderly

No dosage adjustment is required.

Paediatric population

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

Method of administration

For oral use

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.

USE IN SPECIAL POPULATIONS

Use in pregnancy & Lactation:

Pregnancy:

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 labour. Adverse effects (e.g. hypoglycaemia 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, the uteroplacental blood flow and fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus 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.

Lactation:

There are 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.

CONTRA-INDICATIONS

Bisoprolol is contra-indicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients
- Acute heart failure or during episodes of heart failure decompensation requiring i.v. 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
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- Untreated phaeochromocytoma
- Metabolic acidosis

WARNINGS & PRECAUTIONS

Special Warnings

Applies only to chronic heart failure:

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

Applies to all indications:

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.

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 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:

- Insulin dependent diabetes mellitus (type I)
- Severely impaired renal function
- Severely impaired liver function
- Restrictive 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). 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. 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 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 beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicinal products, resulting in bradyarrhythmias, attenuation of 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.

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. dyspnoea, 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 a careful balancing of benefits against 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

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 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

Applies only to hypertension or angina pectoris:

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide propafenone): Effect on atrioventricular 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 medicinal product (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

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

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

Insulin and oral antidiabetic medicinal products: 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: Increase of atrio-ventricular conduction time, reduction in heart rate.

Non-steroidal anti-inflammatory medicinal products (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. norepinephrine, epinephrine): 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 metabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

UNDESIRABLE 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)

Not known (can not be estimated from the available data)

<u>Psychiatric disorders:</u>

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

<u>Nervous system disorders:</u>

Common: dizziness*, headache*.

Rare: syncope

<u>Eye disorders:</u>

Rare: reduced tear flow (to be considered if the patient uses lenses).

Very rare: conjunctivitis.

<u>Ear and labyrinth disorders:</u>

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)

Investigations:

Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT).

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 bisoprolol treatment and supportive and symptomatic treatment is recommended.

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 temporary pacing.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta$_2$-sympathomimetic medicinal products and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties:

Pharmacotherapeutic group: Beta blocking agents, selective.

<u>Mechanism of action</u>

Bisoprolol is a potent highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising 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 $beta_1$-selectivity extends beyond the therapeutic dose range.

Hypertension or angina pectoris:

Bisoprolol is also used for the treatment of hypertension and angina pectoris. As with other Beta1blocking 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 properties:

Absorption

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.

Distribution

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

Biotransformation and Elimination

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 the 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.

INCOMPATIBILITIES

Not applicable

PACKAGING INFORMATION

10 tablets in blister, 3 such blisters in a carton

STORAGE AND HANDLING INSTRUCTIONS

Store in a dry & dark place, at a temperature between 20°C - 25°C.

Manufactured in India by:
Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceuticals Limited)
Plot No. 26A, 27-30, Sector-8A, I.I.E. SIDCUL, Haridwar- 249 403, Uttarakhand.

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Neelam Centre, B Wing, Hind Cycle Road, Worli, Mumbai – 400 030, India
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