20 mm 8 mm 2

Summary of Product Characteristics

BISODAC

Bisoprolol Fumarate Tablets 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg, 10mg

Rx Only

NAME OF THE DRUG PRODUCT

Bisoprolol Fumarate Tablets 1.25 mg
Bisoprolol Fumarate Tablets 2.5 mg
Bisoprolol Fumarate Tablets 3.75 mg
Bisoprolol Fumarate Tablets 5 mg
Bisoprolol Fumarate Tablets 7.5 mg
Bisoprolol Fumarate Tablets 10 mg

(TRADE) NAME OF THE PRODUCT

BISODAC 1.25
BISODAC 2.5
BISODAC 3.75
BISODAC 5
BISODAC 7.5
BISODAC 10

STRENGTH: 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg.

PHARMACEUTICAL DOSAGE FORM: Film-coated tablet

QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Bisoprolol Fumarate Tablets 1.25 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 1.25 mg

Bisoprolol Fumarate Tablets 2.5 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 2.5 mg

Bisoprolol Fumarate Tablets 3.75 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 3.75 mg

Bisoprolol Fumarate Tablets 5 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 5 mg

Bisoprolol Fumarate Tablets 7.5 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 7.5 mg

Bisoprolol Fumarate Tablets 10 mg

Each film-coated tablet contains Bisoprolol Fumarate Ph.Eur. 10 mg

PHARMACEUTICAL FORM

Bisoprolol Fumarate Tablets 1.25 mg: White, circular, biconvex, film-coated tablets debossed with 'P' on one side and '1' on the other side.

Bisoprolol Fumarate Tablets 2.5 mg:* White, circular, biconvex, film-coated tablets debossed with 'P and break line' on one side and '2' on the other side.

Bisoprolol Fumarate Tablets 3.75 mg: White, circular, biconvex, film-coated tablets debossed with 'P and break line' on one side and '3' on the other side.

Bisoprolol Fumarate Tablets 5 mg:* White, circular, biconvex, film-coated tablets debossed with 'P and break line' on one side and '5' on the other side.

Bisoprolol Fumarate Tablets 7.5 mg: White, circular, biconvex, film-coated tablets debossed with 'P and break line' on one side and '7' on the other side.

Bisoprolol Fumarate Tablets 10 mg:* White, circular, biconvex, film-coated tablets debossed with 'P and break line' on one side and '10' on the other side.

****The tablet can be divided into equal halves***

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

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.

Posology:

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 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 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.

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. 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 paediatric experience with bisoprolol, therefore its use cannot be recommended in paediatric patients.

Method of administration:

Bisoprolol tablets should be taken in the morning and can be taken with or without food. They should be swallowed with liquid and should not be chewed.

Contraindications

Bisoprolol is contraindicated in chronic heart failure 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 (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
- Hypersensitivity to bisoprolol or to any of the excipients

Special warnings and precautions for use

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

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.

The initiation and cessation 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
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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 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 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 anaesthesist 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.

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.

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.

Interaction with other medicinal products and other forms of interaction

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 drugs (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 drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): 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

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.

P1521765

A/s : 140 x 340 mm Black

AUROBINDO Packaging Development	Product Name: Bisodac	Component: Leaflet	Item Code: P1521765	Date & Time: 09.02.2021 & 1:00 PM
	Customer / Country: Singapore_Unit-15	Version No.: 03	Reason Of Issue: New	Reviewed / Approved by
Team Leader: Kiran Kumar	Dimensions: 140 x 340 mm	No. of Colours : 01		
Initiator: Shirisha N				
Artist: Vision Graphic Designers	Pharmacode: 21765	21765		
Additional Information : WOS-19-000482				Sign / Date



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.

Pregnancy and lactation

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 fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$-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 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.

Breast-feeding

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

Effects on ability to drive and use machines

In a study with coronary heart disease patients bisoprolol did not impair driving performance. However, 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.

Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Very common (≥1/10)
Common (≥1/100 < 1/10)
Uncommon (≥1/1000 < 1/100)
Rare (≥1/10000 < 1/1000)
Very rare (< 1/10000)

Cardiac disorders:

Very common: bradycardia.

Common: worsening of heart failure.

Uncommon: AV-conduction disturbances.

Investigations:

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

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.

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.

Skin and subcutaneous tissue disorders:

Rare: hypersensitivity reactions (itching, flush, rash).

Very rare: alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness and cramps.

Vascular disorders:

Common: feeling of coldness or numbness in the extremities, hypotension.

Uncommon: orthostatic hypotension.

General disorders:

Common: asthenia, fatigue.

Hepatobiliary disorders:

Rare: hepatitis.

Reproductive system and breast disorders:

Rare: potency disorders.

Psychiatric disorders:

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

Overdose

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness may be occured. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Based on the expected pharmacologic actions and recommendations for other beta-blockers, 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 i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective.

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating 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.

Bisoprolol is already used for the treatment of hypertension and angina.

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.

Clinical efficacy and safety

In total 2647 patients with chronic heart failure were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction ≤ 35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (absolute reduction 5.5%, relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥ 65 years with mild to moderate chronic heart failure (NYHA class II or III) and left ventricular ejection fraction ≤ 35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril- first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

Pharmacokinetic properties

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution

The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

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. Total clearance is approximately 15l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Linearity

The kinetics of bisoprolol are linear and independent of age.

Special population

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 of mild or moderate severity. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

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.

PHARMACEUTICAL PARTICULARS

List of excipients

Cellulose Microcrystalline, Calcium Hydrogen Phosphate Anhydrous, Silica Colloidal Anhydrous, Crospovidone, Magnesium Stearate, Hypromellose 6 cp, Titanium dioxide, Macrogol 400 and Purified Water.

Incompatibilities

Not applicable.

Shelf life

Please refer outer package for expiry date.

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

BISODAC 1.25	
(Bisoprolol Fumarate Tablets 1.25 mg)	-2 x 14's Tablets
BISODAC 2.5	
(Bisoprolol Fumarate Tablets 2.5 mg)	-2 x 14's Tablets
BISODAC 3.75	
(Bisoprolol Fumarate Tablets 3.75 mg)	-2 x 14's Tablets
BISODAC 5	
(Bisoprolol Fumarate Tablets 5 mg)	- 2 x 14's Tablets
BISODAC 7.5	
(Bisoprolol Fumarate Tablets 7.5 mg)	- 2 x 14's Tablets
BISODAC 10	
(Bisoprolol Fumarate Tablets 10 mg)	- 2 x 14's Tablets

The container is a "PA/Alu/PVC-Alu blister" pack.

Not all strengths may be marketed locally

Distributed in Singapore By:

Apotheca Marketing Pte.Ltd.,
63 Hillview Avenue #09-16,
Lam Soon Industrial Building, Singapore 669569.

DATE OF PREPARATION OF THIS LEAFLET

Sep 2020.

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