1.5 Product Information

1.5.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Bisotrol – 5 (Bisoprolol Fumarate Tablets USP 5 mg)

2. Qualitative and quantitative composition

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

3. Pharmaceutical form

Pink coloured, round shaped, biconvex film coated tablets plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Bisoprolol fumarate is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. It is also indicated for the management of angina pectoris.

4.2 Posology and method of administration

The dose of bisoprolol must be individualised to the needs of the patient. The usual starting dose is 5 mg once daily. In some patients 2.5 mg may be an appropriate starting dose (e.g. bronchospastic disease). The dose may be increased to 10 mg and then, if necessary, to 20 mg once daily.

Patients with renal or hepatic impairment
In patients with hepatic impairment (hepatitis or cirrhosis) or renal dysfunction (creatinine clearance less than 40 mL/min) the initial daily dose should be used in dose-titration. Since limited data suggest that bisoprolol is not dialyzable, drug replacement is not necessary in patients undergoing dialysis. Limited data indicate that patients with severe renal impairment (creatinine clearance less than 20ml/min per 1.73m^2) generally should not receive bisoprolol dosages exceeding 10mg once daily.

Geriatric patients
It is not necessary to adjust the dose in the elderly unless there is also significant renal or hepatic dysfunction, in which case dosage may have to be reduced.

1.5 PRODUCT INFORMATION

4.3 Contraindications

Bisoprolol is contraindicated in patients in cardiogenic shock, overt cardiac failure, second or third degree AV block, marked sinus bradycardia, sinoatrial block, bradycardia (heart rate less than 60 beats/min prior to start of therapy), hypotension (systolic blood pressure < 100mmHg), severe bronchial asthma or severe chronic obstructive pulmonary disease, severe forms of peripheral arterial occlusive disease and Raynaud's syndrome, untreated phaeochromocytoma, metabolic acidosis and hypersensitivity to bisoprolol or to any of the excipients.

4.4 Special warnings and precautions for use

WARNINGS

Cardiac failure- In general, beta-blocking agents should be avoided in patients with overt congestive failure. However in some patients with compensated cardiac failure, it may be necessary to utilise these agents. In such situations, they must be used cautiously.

Patients without a history of cardiac failure- Continued depression of the myocardium with beta blockers can, in some patients, precipitate cardiac failure. At the first signs and symptoms of heart failure, discontinuation of bisoprolol should be considered. In some cases bisoprolol therapy can be continued while heart failure is treated with other drugs.

Abrupt cessation of therapy- Exacerbations of angina pectoris and, in some instances, myocardial infarction or ventricular arrhythmia, has been observed in patients with coronary artery disease following abrupt cessation of therapy with betablockers. Such patients should, therefore, be cautioned against interruption or discontinuation of therapy without the physician's advice. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with bisoprolol over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, bisoprolol therapy should be reinstituted, at least temporarily.

Peripheral vascular disease- Beta blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Bronchospastic disease- Patients with bronchospastic pulmonary disease should, in general, not receive beta-blockers. Because of the relative beta -selectivity of bisoprolol, bisoprolol tablets may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since beta1-selectivity is not absolute, the lowest possible dose of bisoprolol tablets should be used. A beta agonist (bronchodilator) should be made available.

Anesthesia and major surgery- If bisoprolol treatment is to be continued perioperatively, particular care should be taken when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.

1.5 PRODUCT INFORMATION

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

Diabetes and hypoglycemia- Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective betablockers may potent iate insul in-induced hypoglycemia and delay recovery of serum glucose levels. Because of its beta1-selectivity, this is less likely with bisoprolol. However, patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities.

Thyrotoxicosis- Beta-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

Others- Patients with psoriasis or with a history of psoriasis should be given beta blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

PRECAUTIONS

Bisoprolol must be used with caution in patients with renal or hepatic impairment, strict fasting, ongoing desensitisation therapy, first degree AV block., Prinzmetal's angina and peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy).

Effect on ability to drive and use machines- As bisoprolol can cause drowsiness, dizziness and fatigue as side effects, these may affect the patient's ability to drive or operate machinery.

Usage in pregnancy and lactation
There are no adequate and well-controlled studies in pregnant women. Bisoprolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Small amounts of bisoprolol (less than 2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when bisoprolol is administered to nursing women.

Usage in paedatrics
Safety and effectiveness in paediatric patients have not been established.

1.5 PRODUCT INFORMATION

Usage in geriatrics
Bisoprolol has been used in elderly patients with hypertension. Response rates and mean decreases in systolic and diastolic blood pressure were similar to the decreases in younger patients in clinical studies. Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose. In general, no disparity in adverse experience reports or dropouts for safety reasons was observed between older and younger patients. Dose adjustment based on age is not necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensive agents: Bisoprolol should not be combined with other beta-blocking agents. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added beta-adrenergic blocking action of bisoprolol may produce excessive reduction of sympathetic activity. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that bisoprolol be discontinued for several days before the withdrawal of clonidine.

Verapamil, diltiazem and disopyramide: Bisoprolol should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists [particularly of the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) classes], or antiarrhythmic agents, such as disopyramide, are used concurrently.

Rifampin: Concurrent use of rifampin increases the metabolic clearance of bisoprolol, shortening its elimination half-life. However, initial dose modification is generally not necessary.

Thiazide diuretics, theophylline and cimetidine: Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics, theophylline and cimetidine.

Warfarin: There was no effect of bisoprolol on prothrobin times in patients on stable doses of warfarin.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimeticagents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoreceptors (e.g. noradrenaline, adrenaline): *C*ombination 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.

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

Insulin and oral antidiabetic drugs: Intensification of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

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.

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.

Others: 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.

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

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Bisoprolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Small amounts of bisoprolol (less than 2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when bisoprolol is administered to nursing women.

4.7 Effects on ability to drive and use machines

As bisoprolol can cause drowsiness, dizziness and fatigue as side effects, these may affect the patient's ability to drive or operate machinery.

1.5 PRODUCT INFORMATION

4.8 Undesirable effects

Adverse of bisoprolol include the following:

Common (>1%and <10%)
Vascular disorders: Feeling of coldness or numbness in the extremities
Central nervous system disorders: Tiredness, exhaustion, dizziness, headache
Gastrointestinal disorders: Nausea, vomiting, diarrhea, constipation

Uncommon (>0.1%and <1%)
General disorders: Muscular weakness and cramps
Cardiac disorders: Bradycardia, disturbance of AV conduction, worsening of heart failure, orthostatic hypotension
Central nervous system disorders: Sleep disturbances, depression
Respiratory, thoracic and mediast inal disorders: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease

Rare (>0.01%and <0.1%)
Central nervous system disorders: Nightmares, hallucinations
Skin and subcutaneous tissue disorders: Hypersensitivity reactions (itching, flush, rash)
Hepatobiliary disorders: Increased liver enzymes (ALAT,ASAT), hepatitis
Metabolism and nutrition disorders: Increased triglycerides
Reproductive system and breast disorders: Potency disorders
Ear and labyrinth disorders: hearing impairment, allergic rhinitis
Eye disorders: Reduced tear flow (to be considered if the patient uses lenses)

Very rare (<0.01%)
Eye disorders: Conjunctivitis, visual disturbances
Skin and subcutaneous tissue disorders: Beta blockers may provoke or worsen psoriasis or induce psoriasis like rash, alopecia
Cardiac disorders: Chest pain

Laboratory abnormalities
In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding. Sporadic liver test abnormalities have been reported. Other laboratory changes included small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreases in WBC and platelets. As with other beta-blockers, ANA conversions have also been reported on bisoprolol.

4.9 Overdose

The most common signs expected with over dosage of a beta-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia. To date, a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported. Bradycardia and/or

hypotension were noted. Sympathomimetic agents were given in some cases, and all patients recovered.

In general, if overdose occurs, bisoprolol therapy should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is not dialyzable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted:

Bradycardia - Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.
Hypotension - IV fluids and vasopressors should be administered. Intravenous glucagon may be useful.
Heart block (second or third degree) – Patients should be carefully monitored and treated with isoproterenol infusion or transvenous cardiac pacemaker insertion, as appropriate.
Congestive heart failure - Initiate conventional therapy (i.e., digitalis, diuretics, inotropic agents, vasodilating agents).
Bronchospasm - Administer bronchodilator therapy such as isoproterenol and/or aminophylline.
Hypoglycemia - Administer IV glucose

5. Pharmacological properties

5.1 Pharmacodynamic properties

Bisoprolol is a beta -selective (cardioselective) β_1 adrenoceptor blocking agent without significant membrane stabilizing or intrinsic Sympathomimetic activities in its therapeutic dose range. Cardioselectivity is not absolute, however, and at higher doses (greater than or equal to 20 mg) bisoprolol also inhibits beta -adrenoceptors, chiefly 2 located in the bronchial and vascular musculature; to retain selectivity it is therefore important to use the lowest effective dose.

The most prominent effect of bisoprolol is the negative chronotropic effect, resulting in a reduction in resting and exercise heart rate. There is a fall in resting and exercise cardiac output with little observed change in stroke volume, and only a small increase in right atrial pressure, or pulmonary capillary wedge pressure at rest or during exercise

The mechanism of action of its antihypertensive effect has not been completely established. Factors that may be involved include:
1) Decreased cardiac output,
2) Inhibition of renin released by the kidneys,
3) Diminution of tonic sympathetic outflow from vasomotor centers in the brain.

In patients with angina, the blockade of β_1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

In normal volunteers, bisoprolol therapy resulted in a reduction of exercise- and isoproterenol-induced tachycardia. The maximal effect occurred within 1 to 4 hours post-dosing. Effects persisted for 24 hours at doses equal to or greater than 5 mg.

Electrophysiology studies have demonstrated that bisoprolol significantly decreases heart rate, increases sinus node recovery time, prolongs AV node refractory periods, and with rapid atrial stimulation, prolongsAVnodal conduction.

Bisoprolol had minimal effect on serum lipids during antihypertensive studies. Changes in total cholesterol averaged +0.8% for bisoprolol-treated patients, and +0.7% for placebo. Changes in triglycerides averaged +19% for bisoprolol-treated patients, and +17% for placebo

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Absorption is not affected by presence of food. Bisoprolol is moderately lipid soluble. The first pass metabolism of bisoprolol is about 20%. Binding to serum proteins is approximately 30%. The plasma elimination half-life is 9 to 12 hours and is slightly longer in elderly patients, in part because of decreased renal function. Bisoprolol is eliminated equally by renal and nonrenal pathways with about 50% of the dose appearing unchanged in the urine and the remainder in the form of inactive metabolites. In humans, the known metabolites are labile or have no known pharmacologic activity. Less than 2% of the dose is excreted in the feces. The pharmacokinetic characteristics of the two enantiomers are similar.

In subjects with creatinine clearance less than 40 mL/min, the plasma half-life is increased approximately threefold compared to healthy subjects. In patients with liver cirrhosis, the rate of elimination of bisoprolol is more variable and significantly slower than that in healthy subjects, with a plasma half-life ranging from 8.3 to 21.7 hours.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipeints

Microcrystalline Cellulose, Dibasic Calcium Phosphate, Pregelatinised Starch, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium Dioxide, Polyethylene Glycol, Polysorbate-80, Purified Water.

6.2 Incompatibilities

1.5 PRODUCT INFORMATION

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in a dry place.

Keep out of reach of children

6.5 Nature and contents of container

Blister Strips of 10 Tablets

7. Marketing authorisation holder

---

8. Marketing authorisation number(s)

---

9. Date of first authorisation/renewal of the authorisation

---

10. Date of revision of the text
