1. Name of the medicinal product

Betafix Tablet 2.5 mg

2. Qualitative and quantitative Composition

Each film-coated tablet contains 2.5 mg bisoprolol fumarate equivalent to 2.12 mg bisoprolol.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Oral Solid Tablets
Brown coloured, round shaped, biconvex, film coated tablets one side breakline and other side plain.

4 Clinical particulars

4.1 Therapeutic indications

Betafix® (Bisoprolol) is indicated in the management of hypertension and in the treatment of angina and heart failure. It may be used alone or in combination with other antihypertensive agents.

4.2 Posology and method of administration

Posology

The dose of Betafix® must be individualized to the needs of the patient. The usual starting dose is Betafix® 5 mg once daily. In some patients, Betafix® 2.5 mg may be an appropriate starting dose. If the antihypertensive effect of Betafix® 5 mg is inadequate, the dose may be increased to Betafix® 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 <40 ml/min), the initial daily dose should be 2.5 mg and caution should be used in dose-titration. Since limited data suggest that Bisoprolol fumarate is not dialyzable, drug replacement is not necessary in patients undergoing dialysis.

Geriatric Patients: It is not necessary to adjust the dose in the elderly, unless there is also significant renal or hepatic dysfunction.

Pediatric Patients: There is no pediatric experience with Bisoprolol.

Method for administration

Oral; taken in the morning with or without food, swallowed whole not chewed

4.3 Contraindications

Bisoprolol is contraindicated in patients with cardiogenic shock, overt cardiac failure, second or third degree AV block, and marked sinus bradycardia.

4.4 Special warnings and precautions for use

Impaired renal or hepatic function:
Use caution in adjusting the dose of Bisoprolol in patients with renal or hepatic impairment.

Risk of anaphylactic reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, accidental, diagnostic or therapeutic.

Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

4.5 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 beta-blocker treatment may lead to profound hypotension and atrioventricular block
- Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease 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 nifedipine: 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-I antiarrhythmic drugs (e.g. disopyramide, quinidine): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased
- 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: Intensification 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 (for further information on general anaesthesia)
- 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
- Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents
- Sympathomimetics that activate both beta-and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-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 beta-blockers. Higher doses of adrenaline may be necessary for treatment of allergic reactions.
- 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.
- Moxisylyte: Possibly causes severe postural 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.

4.6 Pregnancy and lactation

Pregnancy: 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.

Lactation*:* It is not known whether this drug is excreted in human milk. Therefore, breast-feeding is not recommended during administration of Bisoprolol.

4.7 Effects on ability to drive and use machines

It will depend on the individual patient's response to treatment especially at the start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects

Cardiac disorders:
AV-conduction disturbances, worsening of pre-existing heart failure, bradycardia.

Vascular disorders:
feeling of coldness or numbness in the extremities, hypotension, orthostatic hypotension.

Metabolism and nutrition disorders:
Increased triglycerides.

Psychiatric disorders:
sleep disorders, depression, nightmares, hallucinations.

Nervous system disorders:
dizziness*, headache*, syncope

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

Ear and labyrinth disorders:
hearing disorders.

Respiratory disorders:
bronchospasm in patients with bronchial asthma or a history of obstructive airways disease, allergic rhinitis.

Gastrointestinal disorders:
gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

Hepatobiliary disorders:
increased liver enzymes (ALAT, ASAT), hepatitis.

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

Musculoskeletal and connective tissue disorders:
muscular weakness and cramps.

Reproductive system disorders:
potency disorders (reduced libido)

General disorders:
fatigue*, asthenia.

*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1-2 weeks.

4.9 Overdose

The most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia. Only a few cases of overdose 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective.

ATC Code: C07AB07

Bisoprolol fumarate, a cardioselectiveinhibitor of beta (1)-adrenoceptor, has no significant intrinsic sympathomimetic activity or membrane stabilizing activity in its therapeutic dosage. It also exhibits beta (2)-adrenoceptors inhibition and negative chronotropic effect

Mechanism of Action

Bisoprolol blocks the action of the sympathetic nervous system on the heart by blocking the heart's beta-1 adrenergic receptors. Bisoprolol reduces the heart rate & force of contraction of the heart, thus lowers blood pressure.

5.2 Pharmacokinetics

Absorption

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism resulting in an oral bioavailability of about 90%. Peak plasma concentrations occur 2 to 4 hours after oral doses.

Distribution

Bisoprolol is about 30% bound to plasma proteins. Bisoprolol is moderately lipid-soluble.

Metabolism

It is metabolised in the liver

Elimination

It has a plasma elimination half-life of 10 to 12 hours. It is excreted in urine, about 50% as unchanged drug and 50% as metabolites.

6. Pharmaceutical particulars

6. 1 List of excipients

Microcrystalline Cellulose (Type 102)
Anhydrous Calcium Hydrogen Phosphate
Crospovidone
Colloidal Anhydrous Silica
Magnesium Stearate
Instacoat Aqua-III Brown A03R00114

6. 2 Incompatibilities

Bisoprolol fumerate active substances are not incomputable in this preparation. The active material, Febuxostat are not incompatible with excipients used in the formulation too.

It was found that both in long terms stability and accelerated stability studies, the active material, excipients and container closer systems are compatible with formulation.

Excipient's incompatibility literature data:

Microcrystalline Cellulose:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

(Ref. Hand book of pharmaceutical excipients; 6th edition)

Anhydrous Calcium Hydrogen Phosphate:

Dibasic calcium phosphate should not be used to formulate tetracyline antibiotics. The surface of milled anhydrous dibasic calcium phosphate is alkaline and consequently it should not be used with drugs that are sensitive to alkaline pH. However, reports (7,8) suggest there are differences in the surface alkalinity/acidity between the milled and unmilled grades of anhydrous dibasic calcium phosphate; the unmilled form has an acidic surface environment. This difference has important implications for drug stability, particularly when reformulating from, e.g. roller compaction to direct compression, when the particle size of the anhydrous dibasic calcium phosphate might be expected to change.

Dibasic calcium phosphate dihydrate has been reported to be incompatible with a number of drugs and excipients, and many of these incompatibilities are expected to occur with dibasic calcium phosphate, anhydrous; see Calcium phosphate, dibasic

dihydrate. (Ref. Hand book of pharmaceutical excipients,; 6th edition)

Crospovidone

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.
(Ref. Hand book of pharmaceutical excipients; 6th edition)

Colloidal Anhydrous Silica:

Use of the hydrophobic colloidal silica Aerosil reduces the strength of starch-based tablets. (Ref. Hand book of pharmaceutical excipients,; 6th edition)

Magnesium Stearate:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
(Ref. Hand book of pharmaceutical excipients,; 6th edition)

Instacoat Aqua III Brown A03R00114

Not incompatible with Bisoprolol Fumarate and saved for formulation.

6.3 Shelf life

2 years (24 months).

6.4 Special precautions for storage

Store at temperature not exceeding 30° C in a dry place.
Protect from light and moisture.

6.5 Nature and contents of container

Betafix Tablet 2.5 mg are White to off-white, round, shallow biconvex tablets. 5 Tablets are packaged in a blister (Aluminum lid foil 30micron thickness and 3-layer Alu-PVC/OPA film 130-micron thickness as bottom film), each inner carton contains 10 blisters, 3 X 10's

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirement.

7. Marketing authorization holder

Healthcare Pharmaceuticals Ltd.
Gazariapara, Rajendrapur, Gazipur-1703
Bangladesh

8. **MARKETING AUTHORISATION NUMBER (S)**
H2025/CTD11000/24570

9. **DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL**

10. **DATE OF REVISION OF THE TEXT**