ACTIM® Tablets
(Bisoprolol Fumarate)

QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIM® 2.5mg Tablets
Each film coated tablet contains:
Bisoprolol Fumarate (2:1) USP.....2.5mg

ACTIM® 5mg Tablets
Each film coated tablet contains:
Bisoprolol Fumarate (2:1) USP.....5mg

ACTIM® 10mg Tablets
Each film coated tablet contains:
Bisoprolol Fumarate (2:1) USP.....10mg

PHARMACEUTICAL FORM
Tablet

Appearance:
ACTIM® 2.5mg Tablets: Yellow colored, oval shaped, film coated tablet, plain on one side and break line on both side.
ACTIM® 5mg Tablets: Pink colored, round film coated tablet.
ACTIM® 10mg Tablets: Light peach to peach colored, round film coated tablet.

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:
Treatment of stable chronic heart failure with reduced systolic ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Adults: ***Treatment of stable chronic heart failure:*** 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.
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:
- 1.25mg once daily for 1 week, if well tolerated increase to
- 2.5mg once daily for a further week, if well tolerated increase to
- 3.75mg once daily for a further week, if well tolerated increase to
- 5mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5mg once daily for the 4 following weeks, if well tolerated increase to
- 10mg once daily for the maintenance therapy.

The maximum recommended dose is 10mg once daily.
Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter. Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may 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 patient's condition. Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.
Special populations:
Hepatic or renal impairment: There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Titration of the dose in these populations should therefore be made with particular caution.
Elderly: No dosage adjustment is normally required.
Paediatric population: No data is available.
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.

CONTRAINDICATIONS:
Bisoprolol is contraindicated in chronic heart failure patients with:
- Hypersensitivity to the active substance or to any of the excipients.
- Acute heart failure or during episodes of heart failure decompensation requiring IV 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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Special warnings: The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase. 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 transitional worsening of heart condition.
Precautions: The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please. 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 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 hypoglycemia (e.g. tachycardia, palpitations, sweating) can be masked
- Strict fasting
- Ongoing desensitization 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: 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.

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. The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol. In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade. 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 of 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 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 cardio selective (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 airway 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 pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:
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 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 a reduction of heart rate and cardiac output, and to vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of "rebound hypertension".
- ***Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin; flecainide, propafenone):*** Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Combinations to be used with caution:
- ***Calcium antagonists of the dihydropyridine type (e.g. amlodipine, felodipine):*** 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.
- ***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.
- 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.

FERTILITY, PREGNANCY AND LACTATION:
Fertility: Not known
Pregnancy: Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, β-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 β-adrenoceptor blockers is necessary, β1-selective adrenoceptor blockers are preferable. Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and foetal growth is recommended. In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycemia and bradycardia are generally to be expected within the first 3 days.
Breast-feeding: Breast-feeding is not recommended during the administration of bisoprolol.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES:
In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patient's response to treatment, the ability to drive a vehicle or to use machines may be impaired. This should be considered particularly at the start of treatment and upon change of medication or in conjunction with alcohol.

UNDESIRABLE EFFECTS:
The following definitions apply to the frequency terminology used hereafter: Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000) Not known (cannot be estimated from the available data).
Psychiatric disorders: ***Uncommon:*** Sleep disorder, depression. ***Rare:*** Nightmare, hallucination.
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.
Cardiac disorders: ***Very common:*** Bradycardia. ***Common:*** Worsening of pre-existing heart failure. ***Uncommon:*** AV-conduction disturbances.
Vascular disorders: ***Common:*** Feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure. ***Uncommon:*** Orthostatic hypotension.
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 pruritus, flush, rash and angioedema. ***Very rare:*** Alopecia, beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.
Musculoskeletal and connective tissue disorders: ***Uncommon:*** Muscular weakness, muscle cramps.
Reproductive system and breast disorders: ***Rare:*** Erectile dysfunction.
General disorders and administration site conditions: ***Common:*** Asthenia, fatigue.
Investigations: ***Rare:*** Increased triglycerides, increased liver enzymes (ALAT, ASAT).

OVERDOSE:
Symptoms: With overdose (e.g. daily dose of 15mg instead of 7.5mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, 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 (maximum: 2000mg) 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 inter-individual 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 uptitration.
Management: 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-blockers, the following general measures may 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 IV diuretics, inotropic agents, and vasodilating agents. ***Bronchospasm:*** Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline. ***Hypoglycaemia:*** Administer IV glucose. Limited data suggest that bisoprolol is hardly dialysable.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Beta blocking agents, selective, **ATC code:** C07 AB07.
Mechanism of action: Bisoprolol is a potent, highly beta1-selective adrenoreceptor-blocking agent lacking intrinsic sympathomimetic activity and without relevant membrane stabilizing activity. It only shows low affinity to the beta2 receptor of the smooth muscles of bronchi and vessels as well as to the beta2- receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

PHARMACOKINETICS:
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%.
Distribution: 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. The plasma elimination half-life (10-12 hours) provides 24 hours of efficacy following a once-daily dosage.
Biotransformation: 50% is metabolized by the liver to inactive metabolites which are then excreted by the kidneys.
Elimination: Bisoprolol is excreted from the body by two routes. 50% is metabolized by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolized 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.
Other special population: 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±21ng/ml at a daily dose of 10mg and the half-life is 17±5 hours.

PRECLINICAL SAFETY DATA:
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS:

ACTIM® 2.5mg Tablets:
● Maize starch ● Microcrystalline cellulose ● Pre-gelatinized ● Silicon dioxide ● Magnesium stearate ● Hydroxypropyl methyl cellulose ● Titanium dioxide ● Polyethylene glycol ● Talcum powder ● Polyvinyl pyrrolidone ● Tartrazine yellow lake color

ACTIM® 5mg Tablets:
● Maize starch ● Microcrystalline cellulose ● Pre-gelatinized ● Silicon dioxide ● Magnesium stearate ● Hydroxypropyl methyl cellulose ● Titanium dioxide ● Polyethylene glycol ● Talcum powder ● Polyvinyl pyrrolidone ● Yellow iron oxide color ● Red iron oxide color

ACTIM® 10mg Tablets:
● Maize starch ● Microcrystalline cellulose ● Pre-gelatinized ● Silicon dioxide ● Magnesium stearate ● Hydroxypropyl methyl cellulose ● Titanium dioxide ● Polyethylene glycol ● Talcum powder ● Polyvinyl pyrrolidone ● Yellow iron oxide color ● Red iron oxide color

INCOMPATIBILITIES:
Not applicable

SHELF LIFE:
See expiry on the pack.

SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

NATURE AND CONTENTS OF CONTAINER:
ACTIM® 2.5mg Tablets: Alu/PVC blister, pack size 30's.
ACTIM® 5mg Tablets: Alu/PVC blister, pack size 14's.
ACTIM® 10mg Tablets: Alu/PVC blister, pack size 28's.

SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposal of in accordance with local requirements.

DRUG PRODUCT SPECIFICATIONS:
USP Specs.

MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

MARKETING AUTHORISATION NUMBER(S)

ACTIM® 2.5mg Tablets: 045362
ACTIM® 5mg Tablets: 034068
ACTIM® 10mg Tablets: 034069

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ACTIM® 2.5mg Tablets: 16th May, 2007
ACTIM® 5mg Tablets: 20th October, 2004
ACTIM® 10mg Tablets: 20th October, 2004

DATE OF REVISION OF THE TEXT

ایکٹِم ٹیبلٹ

(بسپرولول فیومیریٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی