Package Insert

ACCORD BISOPROLOL 5 (Bisoprolol Fumarate Tablets 5mg)

ACCORD BISOPROLOL 10 (Bisoprolol Fumarate Tablets 10mg)

- **Name and strength of active ingredient**

ACCORD BISOPROLOL 5 : Bisoprolol Fumarate: 5 mg
ACCORD BISOPROLOL 10 : Bisoprolol Fumarate: 10 mg

- **Product Description**

ACCORD BISOPROLOL 5: White to off white, round, biconvex, film coated tablets, debossed 'b2' on one side and breakline on other side. Thickness is between 2.85 mm to 3.55 mm
ACCORD BISOPROLOL 10: White to off white, round, biconvex, film coated tablets, debossed 'b3' on one side and break line on other side. Thickness is between 3.80 mm to 4.80 mm

- **Pharmacodynamics & Pharmacokinetics**

Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective
ATC Code: C07AB07

Bisoprolol is a potent highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and without 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 used for the treatment of hypertension and angina pectoris. As with other Beta- 1-blocking 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.

Pharmacokinetic properties

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.

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

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 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. 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.

- **Indication**

Treatment of high blood pressure (hypertension)
Treatment of coronary heart disease (angina pectoris)
Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

- **Recommended Dosage**

Treatment of hypertension or angina pectoris

In all cases the dose regimen is adjusted individually by your doctor, in particular according to the pulse rate and therapeutic success.
The usual initial dose is 5 mg bisoprolol fumarate once daily. If necessary, the dose may be increased to 10 mg bisoprolol fumarate once daily.
The maximum recommended dose is 20 mg bisoprolol fumarate once daily.
Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

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-blocker, diuretics, and when appropriate cardiac

glycosides. The initiation of treatment of stable chronic heart failure with bisoprolol necessitates a special titration phase.
Precondition for treatment with bisoprolol is stable chronic heart failure without acute failure. It is recommended that the treating physician be experienced in the management of chronic heart failure.
The treatment of stable chronic heart failure with bisoprolol is initiated according to the following titration scheme, individual adaptation may be necessary depending on how well the patient tolerates each dose, i.e. the dose is to be increased only, if the previous dose is well tolerated.

1st week: 1.25 mg bisoprolol fumarate once daily *
2nd week: 2.5 mg bisoprolol fumarate once daily
3rd week: 3.75 mg bisoprolol fumarate once daily *
4th -7th week: 5 mg bisoprolol fumarate once daily
8th -11th week: 7.5 mg bisoprolol fumarate once daily
12th week and beyond: 10 mg bisoprolol fumarate once daily as maintenance treatment

* Bisoprolol 5mg and 10mg is not suitable for initial treatment of stable chronic heart failure. Other approved dosage forms and strengths of bisoprolol fumarate should be used in such cases.

The maximum recommended dose is 10 mg bisoprolol fumarate once daily. Close monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating therapy.

Treatment modification
If during the titration phase or thereafter, transient worsening of heart failure, hypotension or bradycardia occurs, reconsideration of the dosage of 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.

Duration of treatment
Treatment with bisoprolol is generally a long-term therapy.

Do not stop treatment abruptly or change the recommended dose without talking to your doctor first since this might lead to a transitory worsening of heart condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. If discontinuation is necessary, the daily dose is gradually decreased.

Special population

Renal or hepatic impairment:
Treatment of hypertension or angina pectoris: In patients with liver or kidney function disorders of mild to moderate severity no dosage adjustment is normally required. In patients with severe

renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic impairment a daily dose of 10 mg bisoprolol fumarate must not be exceeded.

Treatment of stable chronic heart failure: There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and concomitant hepatic or renal impairment. Titration of the dose in these populations must therefore be made with particular caution.

Elderly:
No dosage adjustment is required.

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

- **Route of Administration**

Oral
Bisoprolol fumarate tablet should be taken in morning and can be taken with food in morning. They should be swallowed in 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
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

- **Warnings & Precautions**

Special warnings:
Applies only to chronic heart failure:
The treatment of stable chronic heart failure with bisoprolol has to be initiated with special titration phase.
Applies to all indications:

Especially in patients with ischemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lad to transition 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 with bisoprolol necessitates regular monitoring. For posology and method of administration please.

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

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. Adrenaline treatment does not always give the expected therapeutic effect.

- first degree AV block
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of 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.
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 thyreotoxicosis may be masked.

- **Interaction with other medicaments**

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 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.
- 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
Applies only to hypertension or angina pectoris:
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 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.
- 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.
- Rifampicin: Slight reduction of the half-life of bisoprolol due to the induction of hepatic drugmetabolising enzymes. Normally no dosage adjustment is necessary.
- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

- **Statement on usage during 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, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended 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 reccomended. 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 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.

- **Adverse Effects/ Undesirable Effects**

The following definitions apply to the frequency terminology used hereafter:
Very common
Common
Uncommon
Rare
Very rare

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

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 (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 and Treatment**

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-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 temporary pacing.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.
Limited data suggest that bisoprolol is hardly dialysable.

- **Storage Conditions**

Do not store above 30°C.

- **Dosage forms and packaging available**

Accord Bisoprolol 5 and 10 is available in Alu-Alu blister pack of 2 x 14 tablets.

- **Name and address of manufacturer**

INTAS PHARMACEUTICALS LIMITED
Plot No. 457 & 458, Village Matoda, Bavla Road
and Plot No. 191/218P, Village: Chacharwadi,
Tal- Sanand, Dist: Ahmedabad, Gujarat, INDIA

- **Date of revision of PI**

20/03/2018