

Package Insert

1. NAME OF THE MEDICINAL PRODUCT

BISOVELL FILM-COATED TABLET 5MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of Bisoprolol Fumarate

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow orange round, convex tablet, plain on one side and breakline on the other side

4. CLINICAL PARTICULARS

4.1. Therapeutic Indication

Treatment of hypertension as well as 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 (for additional information see section 5.1).

4.2. Posology and Method of Administration

For all indications

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 condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. If discontinuation is necessary, the daily dose is gradually decreased.

Bisovell tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

Treatment of hypertension or angina pectoris

For both indications the dosage is 5 mg bisoprolol once daily. If necessary, the dose may be increased to 10 mg bisoprolol once daily.

In all cases the dosage is adjusted individually, in particular according to the pulse rate and therapeutic success.

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 Bisovell 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.

- 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.

Close monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening heart failure is recommended during the titration phase.

The maximum recommended dose is 10 mg once daily.

Occurrence of adverse events may exclude some patients from being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step and the maintenance treatment will be the maximum dose well tolerated by the patient. The treatment may be interrupted if necessary and reintroduced as appropriate.

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.

Special populations

Renal or liver insufficiency

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 insufficiency (creatinine clearance < 20 ml/min) and in patients with severe liver function disorders, it is recommended that a daily dose of 10 mg bisoprolol is not exceeded.

Experience with the use of bisoprolol in renal dialysis patients is limited; however, there is no evidence that the dosage regimen needs to be altered.

Treatment of stable chronic heart failure: There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with concomitant impaired liver or renal function. Uptitration of the dose in these populations should therefore be made with particular caution.

Elderly

No dosage adjustment is required.

Children

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

4.3. Contraindications

Bisoprolol is contraindicated in patients with:

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- Cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- Sick sinus syndrome
- Sinoatrial block
- Symptomatic bradycardia
- Symptomatic hypotension
- Severe bronchial asthma
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated phaeochromocytoma (see section 4.4)
- Metabolic acidosis
- Hypersensitivity to Bisoprolol or to any of the excipients listed in section 6.1

4.4. Special warnings and precautions for use

The initiation of treatment of stable chronic heart failure with bisoprolol necessitates a special titration phase and regular monitoring (see section 4.2).

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 (see section 4.2).

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

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:

- 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.
- AV block of first degree

- 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. Utmost caution must be exercised.
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)

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, Concor 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. 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 pheochromocytoma, bisoprolol must not be administered until after alpha-receptor blockade.

Under treatment with bisoprolol the symptoms of a thyrotoxicosis may be masked.

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 anaesthetist 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.

4.5. Interaction with other drugs, other forms of interactions

Combinations not recommended

For treatment of stable 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.

For all indications

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect 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. methyl dopa, moxonidine, 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

For treatment of 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.

For 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.

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

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

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 (for further information on general anaesthesia see also section 4.4.).

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.

4.6. 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 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, breastfeeding is not recommended during administration of bisoprolol.

4.7. Effects on ability to drive and operate machine

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.

4.8. Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Frequencies are defined as: Very common ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1,000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1,000$), Very rare ($< 1/10,000$), Frequency not known (cannot be estimated from available data).

System organ class	Frequency	Adverse reactions
<i>Cardiac disorders</i>	Very common	Bradycardia in patients with chronic heart failure)
	Common	Worsening of 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)
<i>Investigations</i>	Rare	Increased triglycerides, increased liver enzymes (ALAT, ASAT)
<i>Nervous system disorders</i>	Common	Dizziness*, headache*
	Rare	Syncope
<i>Eye disorders</i>	Rare	Reduced tear flow (to be considered if the patient uses lenses)
	Very rare	Conjunctivitis
<i>Ear and labyrinth disorders</i>	Rare	Hearing disorders
<i>Respiratory, thoracic and mediastinal</i>	Uncommon	Bronchospasm in patients with bronchial asthma or a history of

System organ class	Frequency	Adverse reactions
<i>disorders</i>		obstructive airways disease
	Rare	Allergic rhinitis
<i>Gastrointestinal disorders</i>	Common	Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation
<i>Skin and subcutaneous tissue disorders</i>	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
<i>Musculoskeletal and connective tissue disorders</i>	Uncommon	Muscular weakness and cramps
<i>Vascular disorders</i>	Common	Feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure
<i>General disorders</i>	Common	Asthenia (patients with chronic heart failure), fatigue*
	Uncommon	Asthenia (in patients with hypertension or angina pectoris)
<i>Hepatobiliary disorders</i>	Rare	Hepatitis
<i>Reproductive system and breast disorders</i>	Rare	Erectile dysfunction
<i>Psychiatric disorders</i>	Uncommon	Depression, sleep disorders
	Rare	Nightmares, hallucination

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.

4.9. Overdoses

Symptoms

The most common signs expected with overdosage 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. 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.

Management

In general, if overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment is recommended. Limited data suggest that bisoprolol is hardly dialysable. 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, beta₂-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Bisoprolol is a highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising 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.

Bisoprolol has no pronounced negative inotropic effect. Bisoprolol reaches its maximal effect 3– 4 hours after oral administration. As a result of its half-life of 10 – 12 hours bisoprolol has a 24-hour effect. The maximal antihypertensive effect of bisoprolol is generally reached after 2 weeks. Through blockade of cardiac Beta-receptors bisoprolol depresses the response to sympathoadrenergic activity. This causes a decrease in heart rate and in contractility and thus a reduction of myocardial oxygen consumption which is the desired effect in angina pectoris with underlying coronary heart disease.

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. Among others, the depression of plasma renin activity is discussed as a mechanism of action underlying the antihypertensive effect of beta-blockers.

Clinical efficacy and safety

In total 2647 patients 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% (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 (CHF; NYHA class II or III) and left ventricular ejection fraction $\leq 35\%$, 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 also be used in elderly chronic heart failure patients with mild to moderate disease.

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

5.2. 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 15 l/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

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.

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.

5.3. Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity/mutagenicity or carcinogenicity. In reproduction toxicology studies, bisoprolol had no influence on fertility or on general reproduction performance.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

- Maize starch
- Calcium hydrogen phosphate dihydrate
- Microcrystalline cellulose PH 102
- Crospovidone
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating:

- Kollicoat[®] protect
- Titanium dioxide
- Talc
- FD&C yellow no. 6 aluminium lake
- FD&C yellow no. 10 aluminium lake

6.2. Incompatibilities

Not Available

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store at or below 30°C

6.5. Nature and contents of container

Box, 3 blisters forming of Aluhard and clear PVC/PVDC @ 10 film-coated tablets

6.6. Instruction for use/handling, and disposal (if appropriate)

No special requirements

7. Name and Address of Product Registrant

Novem Healthcare Pte Ltd

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Singapore 536209

8. DATE OF REVISION OF THE TEXT

March 27th, 2023