PACKAGE INSERT TEMPLATE FOR BISOPROLOL TABLET

Brand or Product Name
[Product name] Tablet 2.5mg
[Product name] Tablet 5mg
[Product name] Tablet 10mg

Name and Strength of Active Substance(s)

Bisoprolol fumarate/hemifumarate …mg equivalent to bisoprolol ….mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film-coated dispersible tablets marked '10' on one side

Pharmacodynamics
Bisoprolol fumarate, a cardioselective inhibitor 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

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

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Indication

For 5mg & 10mg

- 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

For 2.5mg

- 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 hemifumarate once daily. If necessary, the dose may be increased to 10 mg bisoprolol hemifumarate once daily.
The maximum recommended dose is 20 mg bisoprolol hemifumarate 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 hemifumarate once daily *
2nd week:	2.5	mg	bisoprolol hemifumarate once daily
3rd week:	3.75	mg	bisoprolol hemifumarate once daily *
4th -7th week:	5	mg	bisoprolol hemifumarate once daily
8th -11th week:	7.5	mg	bisoprolol hemifumarate once daily
12th week and beyond:	10	mg	bisoprolol hemifumarate once daily as maintenance treatment

* Bisoprolol 5mg and 10mg is not suitable for initial treatment of stable chronic heart failure. Lower strengths are available for this purpose.

The maximum recommended dose is 10 mg bisoprolol hemifumarate 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 populations

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 hemifumarate 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.

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

Contraindications
Bisoprolol must not be used in patients with:

- acute heart failure or during episodes of heart failure decompensation requiring intravenous therapy with substances increasing the contractility of the heart
- shock induced by disorders of cardiac function (cardiogenic shock)
- severe disturbances of atrioventricular conduction (second or third degree AV block) without a pacemaker
- sick sinus syndrome
- sinoatrial block
- slowed heart rate, causing symptoms (symptomatic bradycardia)
- decreased blood pressure, causing symptoms (symptomatic hypotension)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or Raynaud syndrome
- untreated tumours of the adrenal gland (phaeochromocytoma)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

Warnings and Precautions
The following section describes when bisoprolol must be used with special caution:

- diabetes mellitus with extremely fluctuating blood glucose levels: symptoms of markedly reduced blood glucose (hypoglycaemia) such as tachycardia, palpitations or sweating can be masked
- strict fasting

- ongoing desensitisation therapy,
- mild disturbances of atrioventricular conduction (first degree AV block)
- disturbed blood flow in the coronary vessels due to vasospasms (Prinzmetal angina)
- peripheral arterial occlusive disease (aggravation of symptoms may occur especially when starting therapy)
- patients with psoriasis or with a personal history of psoriasis

Respiratory system: In bronchial asthma or other symptomatic chronic obstructive pulmonary diseases concomitant bronchodilator therapy is indicated. An increase in airway resistance may occasionally occur in patients with asthma, requiring a higher dose of beta2sympathomimetics.

Allergic reactions: Beta-blockers, including bisoprolol, may increase the sensitivity to allergens and the severity of anaphylactic reactions because the adrenergic counter regulation under beta-blockade may be alleviated. Treatment with adrenaline may not always yield the expected therapeutic effect.

General anaesthesia: In patients undergoing general anaesthesia the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw bisoprolol before surgery, this should be done gradually and completed about 48 hours prior to anaesthesia.

Phaeochromocytoma: In patients with a tumour of the adrenal gland (phaeochromocytoma) bisoprolol may only be administered after previous alpha-receptor blockade.

Thyrotoxicosis: Under treatment with bisoprolol the symptoms of a thyroid hyperfunction (thyrotoxicosis) may be masked.

Special populations

So far no sufficient therapeutic experience is available for bisoprolol in patients with heart failure and concomitant insulin dependent type I diabetes mellitus, severely impaired kidney function, severely impaired hepatic function, restrictive cardiomyopathy, congenital heart diseases or haemodynamically relevant organic valvular heart disease. No sufficient therapeutic experience is available either in patients with heart failure and myocardial infarction within the last 3 months.

There is insufficient experience with bisoprolol in children, therefore the use of bisoprolol cannot be recommended for children.

Effects on the 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.

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Interactions with Other Medicaments

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 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.

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

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• 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.

Statement on Usage During Pregnancy and Lactation
Pregnancy
Bisoprolol should be given only if the potential benefit justifies the potential risk to the fetus

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, β_1-selective adrenoceptor blockers are preferable.

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, breastfeeding is not recommended during administration of bisoprolol.

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Adverse Effects / 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.*

Overdose and Treatment

Symptoms
The most frequent signs of bisoprolol overdose include slow heart rate (bradycardia), marked drop in blood pressure, acute heart failure, hypoglycaemia and bronchospasm.

Treatment
In general, if overdose occurs, bisoprolol treatment is stopped and supportive and symptomatic treatment is provided.

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

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Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

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