4.2 Posology and method of administration

_Treatment of hypertension or angina pectoris_

The maximum recommended dose is 20 mg once daily.

_Treatment of stable chronic heart failure_

It is recommended that the treating physician 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 maximum recommended dose is 10 mg once daily.

_Special Populations_

_Renal or liver impairment_

_applies only to hypertension or angina pectoris:_

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

_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,
- second or third degree AV block,
- sick sinus syndrome,
- sinoatrial block,
- symptomatic bradycardia,
- symptomatic hypotension,
- severe bronchial asthma or severe chronic obstructive pulmonary disease.
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome,
- untreated phaeochromocytoma (see section 4.4),
- metabolic acidosis.

{Tradename} is contra-indicated in patients with hypersensitivity to bisoprolol or to any of the excipients.

4.4 Special warnings and precautions for use

applies only to CHF:

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase.

applies to all indications:

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

applies only to CHF:

The initiation and cessation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring.

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin-dependent diabetes mellitus (type 1)
- 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

- diabetes mellitus showing 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 may not always yield the expected therapeutic effect,
- First degree AV block,
- Prinzmetal's angina,
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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 the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Combinations not recommended**

*applies only to CHF:*

Class-I antiarrhythmic drugs: 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 effect 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: Concomitant use of centrally-acting antihypertensive drugs may lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal may increase the risk of 'rebound hypertension'.

**Combinations to be used with caution**

*applies only to hypertension or angina pectoris:*

Class-I antiarrhythmic drugs: Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

*applies to all indications:*

Calcium antagonists of the dihydropyridine type: 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: 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-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

Digitalis glycosides: Increase of atrio-ventricular conduction time, reduction in heart rate.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

Beta-sympathomimetics: Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors: Combination with bisoprolol may lead to blood pressure increase.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential may increase the risk of hypotension.

**Combinations to be considered**

Mefloquine: increased risk of bradycardia.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

*Tradename* is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and the 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 hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

**Lactation**

Breastfeeding is not recommended during administration of *Tradename*.
4.7 Effects on ability to drive and use machines

Depending on the individual patients response to treatment the ability to drive a vehicle or to use machines may be impaired. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects

Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%).

Investigations
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT)

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)

Nervous system disorders
Common: dizziness*, headache*
Rare: syncope

Eye disorders
Rare: reduced tear flow
Very rare: conjunctivitis

Ear and labyrinth disorders
 Rare: hearing disorders

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

Skin and subcutaneous tissue disorders
Rare: hypersensitivity reactions such as itching, flush, rash
Very rare: alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders
Uncommon: muscle weakness, muscle cramps

Vascular disorders
Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure

General disorders
Common: asthenia (patients with chronic heart failure), fatigue*
Uncommon: asthenia (in patients with hypertension or angina pectoris)
**Hepatobilary disorders**
*Rare:* hepatitis

**Reproductive system and breast disorders**
*Rare:* potency disorders

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

*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 **Overdose**

**Symptoms**

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. 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, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Limited data suggest that bisoprolol is hardly dialysable.