Concor®

Bisoprolol fumarate

Concor 2.5 mg, film-coated tablets

Concor 5 mg, film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Concor 2.5 mg: Each tablet contains 2.5 mg bisoprolol fumarate.

Concor 5 mg: Each tablet contains 5 mg bisoprolol fumarate.

PHARMACEUTICAL FORM

Film-coated tablet.

Concor 2.5 mg: White, heart-shaped, scored and film-coated tablets.

Concor 5 mg: Yellowish white, heart-shaped, scored and film-coated tablets.

CLINICAL PARTICULARS

Therapeutic indications

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 *Pharmacodynamic properties*).

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.

Concor 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 Concor 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.

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 *Special warnings and precautions for use*)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

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 *Posology and method of administration*).

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 *Posology and method of administration*).

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 liver 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 may not always give 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 phaeochromocytoma 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 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.

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.

Pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/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 foetus 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 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.

Interaction with other medicinal products and other forms of interaction

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 (e.g. clonidine, methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the 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 (e.g. 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: Intensification 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 (for further information on general anaesthesia see section *Special warnings and precautions for use*).

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

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

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

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine): 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 of hypertensive crisis.

Undesirable effects

Very common (≥ 10%)
Common (≥ 1% to < 10%)
Uncommon (≥ 0.1% to < 1%)
Rare (≥ 0.01% to < 0.1%)
Very rare (< 0.01%)
Frequency not known (cannot be estimated from available data)

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 (to be considered if the patient uses contact lenses)
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 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:	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)

Hepatobiliary disorders

Rare:	hepatitis

Reproductive system and breast disorders

Rare:	erectile dysfunction

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.

Overdose

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.

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 with chronic heart failure 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 $\leq$ 35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (absolute reduction 5.5%, 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 (NYHA class II or III) and left ventricular ejection fraction ≤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 be used in elderly chronic heart failure patients with mild to moderate disease.

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

Pharmacokinetic properties

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. 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.

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 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.

The kinetics of bisoprolol are linear and independent of age.

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.

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 gain) and embryo/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

PHARMACEUTICAL PARTICULARS

Special precautions for storage

Store at or below 30ºC

Nature and contents of container

The container is a blister, which is made of an aluminium base foil and an aluminium cover foil.

MANUFACTURER

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