Concor® 5 mg / Concor® 10 mg

Active ingredient: bisoprolol hemifumarate

1. NAME OF THE MEDICINAL PRODUCT

Concor 5 mg film-coated tablet
Concor 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concor 5 mg: Each tablet contains 5 mg bisoprolol fumarate.
Concor 10 mg: Each tablet contains 10 mg bisoprolol fumarate.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet
Visual appearance:
Concor 5 mg: yellowish white, hexa-shaped, film-coated tablets scored on both sides.
Concor 10 mg: pale orange-light orange, heart-shaped, film-coated tablets scored on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- High blood pressure (hypertension)
- Coronary heart disease (Angina pectoris as basic treatment, not in angina crisis)
- Treatment of stable chronic heart failure with reduce systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Posology
Treatment of hypertension or coronary heart disease (Angina pectoris)
Adults: For both indications the dosage 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 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.
Patients should be stable (without acute failure) when bisoprolol treatment is initiated.
It is recommended that the treating physician be experienced in the management of chronic heart failure.
Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Titration phase
The treatment of stable chronic heart failure with bisoprolol requires a titration phase. The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 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.

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

Treatment modification
If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.
In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the 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.
If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.

Duration of therapy
Treatment with bisoprolol is generally a long-term therapy.
The treatment with bisoprolol must not be stopped abruptly since the might lead to a transitory worsening of condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. Gradual reduction of the dosage is recommended.

Renal or liver impairment
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 liver function disorders it is recommended that a daily dose of 10 mg bisoprolol fumarate 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.
Stable chronic heart failure
There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic of renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly
No dosage adjustment is required.

Paediatric population
There is no paediatric experience with bisoprolol, therefore its use cannot be recommended in paediatric patients.

Method of administration
Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

4.3 Contraindications

Bisoprolol is contra-indicated 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 (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 see section 6.1.

4.4 Special warnings and precautions for use

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2)
Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless deadly 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.
The initiation and cessation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the posology and method of administration see section 4.2.
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

Bisoprolol must be used with caution in

- diabetes mellitus showing 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 β-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,
- First degree AV block,
- Prinzmetal's angina,
- peripheral arterial occlusive disease. Intensification of complaints may occur especially when starting therapy.

Patients with psoriasis or with a history of psoriasis should only be given β-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 α-receptor blockade.
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.
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. When such reasons exist, Concor may be used with caution.
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 β2-stimulants may have to be increased.

4.5 Interaction with other medicinal products and other forms of interaction

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 atrio-ventricular block.
Central-acting antihypertensive drugs (e.g. methyldopa, moxonidine, reserpine, 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, vasodilatation). Abrupt withdrawal, particular if prior to β-blocker discontinuation, may increase the 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 (e.g. 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 –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 β-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 β-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 4.4.).
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.
β-sympathomimetics (e.g. isoprenaline, ociprenaline, 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

Combination 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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, β1-selective adrenoceptor blockers are preferable, Concor 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.

Breastfeeding
There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants.
Therefore, breastfeeding is not recommended during administration of Concor.

4.7 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 is to 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.
Very common (≥ 1/10), Common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10 000, < 1/1000), very rare (< 1/10 000).

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

Cardiac disorders
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)

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 itching, flush, rash
Very rare: alopecia, β-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 (in patients with chronic heart failure),
Uncommon: hypotension (in patients with hypertension or angina pectoris), orthostatic hypotension (in patients with chronic heart failure).

General disorders
Common: asthenia (in 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: potency disorders

Psychiatric disorders
Uncommon: depression, sleep disorders
Rare: nightmares, hallucinations
*These symptoms especially occur at the beginning of the therapy of hypertension or angina pectoris.
They are generally mild and usually disappear within 1-2 weeks.

4.9 Overdose

Symptoms
The most common signs expected with overdose of a β-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. Therefore it's mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme illustrated in section 4.2.

Management
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Bisoprolol is a β1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows very low affinity to the β2-receptor of the smooth muscles of bronchi and vessels as well as to the β2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β2-mediated metabolic effects. Its β1-selectivity extends beyond the therapeutic dose range.
Bisoprolol has no pronounced negative inotropic effect.
In acute administration in patients with coronary heart disease without chronic heart failure, bisoprolol reduces the heart rate and stroke volume, thus reducing 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 β-blockers.
Bisoprolol depresses the response to sympathoadrenergic activity through blockade of cardiac β-receptors. 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.

5.2 Pharmacokinetic properties

Absorption
Bisoprolol is almost completely (>90%) absorbed from the gastrointestinal tract and, because of its small first pass metabolism of approximately 10%, it has an absolute bioavailability of approximately 90% after oral administration.

Distribution
The volume of distribution is 3,5 l/kg. Binding to plasma proteins is approximately 30%.

Bio-transformation and elimination
Bisoprolol is removed from the organism via two equally effective clearance routes: 50% is transformed into inactive metabolites in the liver with excretion of the metabolites via the kidneys. The remaining 50% are excreted as unchanged substance via the kidneys. Therefore, bisoprolol generally requires no dosage adjustment in patients with liver or kidney function disorders of mild or moderate severity since the elimination takes place to the same extent in the kidneys and the liver.
Bisoprolol reached maximal effect 3-4 hours after oral administration. The plasma elimination half-life of 10-12 hours provides 24 hours efficacy following a once daily dosing. The maximal blood pressure lowering effect of bisoprolol is generally reached after 2 weeks.

Linearity
Bisoprolol has linear, age-independent kinetics.
Social population
In patients with chronic heart failure (NYHA class 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.
The pharmacokinetics in patients with stable chronic heart failure and concomitant impaired liver or renal function have not been studied.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity/ mutagenicity or carcinogenicity

Reproduction toxicity
In reproduction toxicology studies bisoprolol had no influence on fertility or on general reproduction performance.
Like other β-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight gain) 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

Table core:
Silica, colloidal anhydrous
Magnesium stearate
Crospovidone
Microcrystalline cellulose
Maize starch
Calcium hydrogen phosphate, anhydrous

Film coating:
Iron oxide yellow (E172)
Dimethicone
Macrogol 400
Titanium dioxide (E171)
Hypromellose
Concor 10 mg:
Contains iron oxide red (E172) in the film coating in addition to the above excipients.

6.2 Shelf life

36 months.

6.3 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Nature of container: aluminium/aluminium blister
Pack size: Carton box containing 3 strips, with package insert leaflet. Each strip contains 10 tablets.

6.6 Special precautions for disposal

No special requirements.

7. Manufactured by:

Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany

8. Marketing authorisation holder

Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany

9. Date of information

23 May 2014

This is a medicine

- A medicine is a product which affects your health and its consumption, contrary to instructions, is dangerous for you.
- Closely follow your doctor's prescription, the method of use and the instructionsof the pharmacist who sold the product.
- Your doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not interrupt the period of treatment prescribed without your doctor's permission
- Do not repeat the same prescription without consulting your doctor

Keep medicines out of reach of children.