1. NAME OF THE MEDICINAL PRODUCT

Concor 5 mg film-coated tablets

Concor 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Bisoprolol fumarate

Concor 5 mg:
One film-coated tablet contains 5 mg bisoprolol fumarate.

Concor 10 mg:
One film-coated tablet contains 10 mg bisoprolol fumarate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Concor 5 mg are yellowish white, heart-shaped film-coated tablets with a dividing score.
Concor 10 mg are pale-orange light-orange, heart-shaped film-coated tablets with a dividing score.

The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension
- Coronary heart disease (angina pectoris)

4.2 Posology and method of administration

Posology

Treatment should generally be initiated gradually with low doses, which are then increased slowly. In all cases the dosage should be adjusted individually, above all in accordance with the pulse rate and therapeutic success.

Hypertension
The recommended dosage is 5 mg bisoprolol fumarate once daily.
With milder forms of hypertension (diastolic blood pressure up to 105 mmHg), therapy with 2.5 mg once daily may be adequate.

If necessary, the dosage may be increased to 10 mg once daily. A further dosage increase is justified only in exceptional cases.

The maximum recommended dosage is 20 mg once daily.

Coronary heart disease (angina pectoris)
The recommended dosage is 5 mg bisoprolol fumarate once daily.
If necessary, the dosage may be increased to 10 mg once daily. A further dosage increase is justified only in exceptional cases.

The maximum recommended dosage is 20 mg once daily.

Dosage in hepatic and/or renal insufficiency
In patients with liver or kidney function disorders of mild to moderate severity, dosage adjustment is generally not required. In patients with severe kidney function disorders (creatinine clearance < 20 ml/min) and in patients with severely impaired liver function, a daily dose of 10 mg bisoprolol fumarate should not be exceeded.
Experience with the use of bisoprolol in dialysis patients is limited and there are no indications of the necessity to alter the dose regimen.

Elderly people
No dose adjustment is required in elderly patients.

Paediatric population
Paediatric experience with bisoprolol does not exist, therefore use cannot be recommended in paediatric patients.

Method of administration

The film-coated tablets are to be swallowed whole with some liquid in the morning, either before, during or after breakfast.

Duration of therapy

The duration of therapy is not limited. It depends upon the nature and severity of the disease.

Concor therapy should not be stopped abruptly, particularly in patients with coronary heart disease, as this may lead to acute deterioration of the patient's state of health. If discontinuation of therapy becomes necessary, the dose should be gradually reduced (e.g. halving of the dose at weekly intervals).

4.3. Contraindications

Concor must not be used in patients with:

- acute heart failure or during episodes of heart-failure decompensation requiring IV 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 or Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis
- known hypersensitivity to bisoprolol or to any of the excipients (see section 6.1)

4.4 Special warnings and precautions for use

Concor therapy must not be stopped abruptly, particularly in patients with coronary heart disease, as this may lead to transient deterioration of the patient's state of health (see section 4.2).

Concor therapy must proceed with caution in patients with hypertension or angina pectoris and concomitant heart failure.

Concor may only be used with special caution in:

- diabetes mellitus with extremely fluctuating blood glucose levels; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) may be masked
- strict fasting
- ongoing desensitisation therapy

As with other beta-blockers, bisoprolol may increase both the sensitivity to allergens and the severity of anaphylactic reactions. Adrenaline may not always yield the desired therapeutic effect in these cases.

- First-degree AV block
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Despite its high $beta_1$-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy)

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, generally these should be avoided in patients with obstructive airway diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, Concor may be used with caution. In bronchial asthma or other chronic obstructive pulmonary disorders that can cause symptoms, concomitant bronchodilating therapy is indicated. Occasionally an increase of airway resistance may occur in asthma patients, requiring a higher dose of a $beta_2$-sympathomimetic agent.

<u>General anaesthesia</u>
In patients undergoing general anaesthesia, beta-blockers reduce the incidence of arrhythmias and myocardial ischemia during induction, intubation, and postoperatively. It is currently recommended that ongoing beta-blocker therapy be continued peri-operatively. The anaesthetist must be informed that the patient is being treated with beta-blockers as

this may lead to potential interactions with other pharmaceuticals, resulting in bradyarrhythmia, attenuation of reflex tachycardia and decreased reflex ability to compensate for blood loss. If discontinuation of beta-blocker therapy prior to surgery is necessary, treatment should be tapered gradually and be discontinued altogether about 48 hours prior to anaesthesia.

In patients with a history of psoriasis, beta-blockers (e.g. bisoprolol) should only be prescribed after carefully assessing the risk-benefit ratio.

In patients with phaeochromocytoma, bisoprolol must not be administered until after alpha-receptor blockade.

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

The use of Concor may lead to a false positive drug screen.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration with the following drugs is not recommended:

Calcium antagonists of the verapamil type and to a lesser extent those of the diltiazem type: Negative influence on contractility and atrioventricular conduction. Intravenous administration of calcium antagonists of the verapamil type may lead to profound hypotension and atrioventricular block in patients on beta-blocker treatment.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, reserpine): Combination therapy with centrally-acting antihypertensive agents may lead to worsening of heart failure due to reduction of the central sympathetic tone (reduction of pulse rate and ejection fraction, vasodilatation). Abrupt discontinuation, particularly prior to termination of beta-blockade may increase the risk of rebound hypertension.

Concomitant administration with the following drugs only with caution:

Class I antiarrhythmic agents (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone): Effect on atrioventricular conduction time and negative inotropic effect may be potentiated.

Calcium antagonists of the dihydropyridine type (e.g. nifedipine): In concomitant administration, the risk of hypotension and impairment of ventricular pumping function in heart failure patients cannot be excluded.

Class III antiarrhythmic agents (e.g. amiodarone): Effect on atrioventricular conduction time may be potentiated.

Parasympathomimetic agents: Combination therapy may increase the atrioventricular conduction time and the risk of bradycardia.

Topical application of beta-blockers (e.g. as in eyedrops for glaucoma treatment) may potentiate the systemic effect of bisoprolol.

Insulin and oral antidiabetic agents: Increase of blood glucose lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of reflex tachycardia and increased risk of hypotension (see also section 4.4)

Digitalis glycosides: Reduction in heart rate, increase of atrioventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): Decreased hypotensive effect.

Beta-sympathomimetic agents (e.g. dobutamine, orciprenaline): Combination with bisoprolol may reduce the effect of both agents. Higher doses of adrenaline may be required for treatment of allergic reactions.

Sympathomimetic agents that activate alpha- and beta-receptors (e.g. adrenaline, noradrenaline): Potential increase in blood pressure and exacerbation of intermittent claudication. Such interactions are more likely in non-selective beta-blockers.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agents: Increased hypotensive effect.

Notes to be taken into account in concomitant administration with the following:

Mefloquine: Increased risk of bradycardia.

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blocker 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/neonate. In general, beta-blockers reduce placental perfusion possibly leading to intra-uterine growth retardation, intrauterine death, miscarriage or early labour. Adverse events (e.g. hypoglycaemia and bradycardia) may occur in the foetus and the neonate. If beta-blocker treatment is necessary, $beta_1$-selective beta-blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, utero-placental blood flow and foetal growth must be monitored. In the case of harmful effects on pregnancy or the foetus, alternative therapeutic measures should be considered. The neonate must be monitored closely. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days of life.

Breastfeeding

It is not known whether bisoprolol passes into human breast milk. Therefore, breast-feeding is not recommended during bisoprolol therapy.

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 individually varying reactions to the medicinal product, the ability to drive a vehicle or to use machinery may be impaired. This needs to be considered particularly at the start of bisoprolol treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The assessment of adverse reactions is based on the following frequency grouping:

Common:	≥1/100 to <1/10
Uncommon:	≥1/1,000 to <1/100
Rare:	≥1/10,000 to <1/1,000
Very rare:	<1/10,000
Not known:	Frequency cannot be estimated from the available data

<u>Investigations</u>	
Rare	Increased triglycerides, increased liver enzymes (ALAT, ASAT)
<u>Cardiac disorders,</u>	
Uncommon	Bradycardia, AV-conduction disturbances, worsening of pre-existing heart failure
<u>Nervous system disorders</u>	
Common	Dizziness*, headache*
Rare	Syncope
<u>Eye disorders</u>	
Rare	Reduced tear flow (to be considered if the patient uses contact lenses)
Very rare	Conjunctivitis
<u>Ear and labyrinth disorders</u>	
Rare	Hearing disorders
<u>Respiratory, thoracic and mediastinal disorders</u>	
Uncommon	Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease
Rare	Allergic rhinitis
<u>Gastrointestinal disorders</u>	
Common	Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation
<u>Skin and subcutaneous tissue disorders</u>	
Rare	Hypersensitivity reactions (pruritus, flush, rash and angioedema)
Very rare	Hair loss. Beta-blockers can 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
Uncommon	Hypotension

General disorders and administration site conditions

Common	Fatigue*
Uncommon	Asthenia

Hepatobiliary disorders

Rare	Hepatitis

Reproductive system and breast disorders

Rare	Erectile dysfunction

Psychiatric disorders

Uncommon	Depression, sleep disorder
Rare	Nightmares, hallucination

*These symptoms occur particularly at the start of treatment. They are generally mild and usually disappear within 1-2 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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Division de la Pharmacie et des Médicaments de la Direction de la Santé à Luxembourg
pharmacovigilance@ms.etat.lu
Tel: (+352) 2478 5592
Link to the form:
https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html

4.9 Overdose

a) Symptoms of intoxication

The most common signs of overdose with a beta-blocker are bradycardia, hypotension, bronchospasm, acute heart failure, and hypoglycaemia. To date a few cases of overdosage (maximum 2,000 mg) with bisoprolol have been reported in patients with hypertension and/or coronary heart disease. These patients exhibited bradycardia and hypotension. All patients recovered.

The sensitivity to high single doses of bisoprolol varies greatly between individuals. The probability that patients with heart failure could react sensitively should be considered.

b) Treatment of intoxication

In general, if overdose occurs, biosoprolol therapy should be stopped and supportive and symptomatic treatment should be initiated. The limited data available suggest that bisoprolol is hardly dialysable. Based upon the expected pharmacological actions and recommendations for other beta-blockers, the following general measures should be carried out if clinically required.

Bradycardia: Intravenous administration of atropine. In inadequate response, orciprenaline or another agent with positive chronotropic properties may be given cautiously. Under certain circumstances, transvenous pacemaker implantation may become necessary.

Hypotension: Intravenous fluid replacement and administration of vasopressors. Intravenous glucagon may also be useful.

AV block (second or third degree): Patients should be monitored carefully and treated with orciprenaline infusions. If necessary, a transient pacemaker should be implanted.

Acute worsening of heart failure: Intravenous administration of diuretics, positive inotropic agents, as well as vasodilators.

Bronchospasm: Administration of bronchodilators such as orciprenaline, $beta_2$-sympathomimetic agents and/or aminophylline.

Hypoglycaemia: Intravenous administration of glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective beta-blocker
ATC code: C07AB07

Mechanism of action

Bisoprolol is a highly $beta_1$-selective adrenoceptor-blocking agent with neither intrinsic stimulating nor relevant membrane-stabilising activity. It shows only low affinity to the $beta_2$-receptors of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors of enzymatic metabolic regulation. Therefore, bisoprolol is generally not

expected to influence airway resistance and $beta_2$-mediated metabolic processes. Its $beta_1$-selectivity extends beyond the therapeutic dose range. Bisoprolol has no pronounced negative inotropic activity.

The maximum effect of bisoprolol sets in 3-4 hours after oral administration. The plasma elimination half-life of 10-12 hours results in 24-hour efficacy when administered once daily. In general, the maximum antihypertensive effect of bisoprolol is achieved after 2 weeks of treatment.

In acute therapy of patients with coronary heart disease without chronic heart failure, bisoprolol decreases the heart rate and reduces the stroke volume resulting in diminished ejection fraction and oxygen consumption. In chronic therapy the initially increased peripheral resistance decreases. Among others depression of plasma renin activity is discussed as a mechanism of action underlying the antihypertensive effect of beta-blockers.

Bisoprolol depresses the response to sympatho-adrenergic activity through blockade of cardiac beta-receptors. This causes a decrease in heart rate and in contractility and thus a reduction of myocardial oxygen consumption. The latter represents the desired effect in patients with angina pectoris and underlying coronary heart disease.

5.2 Pharmacokinetic properties

Absorption

After intake, bisoprolol is absorbed almost completely (> 90%) from the gastrointestinal tract. Absorption is independent of food intake.
The first pass effect is ≤10%. This results in an absolute bioavailability of approximately 90% after oral administration.

Distribution

The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg.

Biotransformation and elimination

Bisoprolol is excreted from the body by two equally effective clearance routes with 50% being metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in unmetabolised form. Since elimination takes place in the kidneys and the liver to the same extent, dosage adjustment is generally not required for patients with impaired liver or kidney function of mild or moderate severity (see also section 4.2 "Dosage in hepatic and/or renal insufficiency").
Total clearance is approximately 15 l/h. The plasma elimination half-life is 10-12 hours (see also section 5.1).

Linearity

The pharmacokinetics of bisoprolol are linear and independent of age.

5.3 Preclinical safety data

Based on conventional studies on safety pharmacology, chronic toxicity, mutagenicity or carcinogenicity, preclinical data reveal no special risks for humans.

Reproduction
Reproduction toxicity studies with bisoprolol revealed no adverse effect on fertility or reproductive behaviour.

As known with other beta-blockers, certain maternal (decreased food intake and weight loss) and embryonal/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development), but not teratogenicity were observed with high doses of bisoprolol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concor 5 mg / 10 mg film-coated tablets

Tablet core: Colloidal silicon dioxide, magnesium stearate (Ph.Eur.); crospovidone, microcrystalline cellulose; corn starch; calcium hydrogen phosphate.

Film-coating: Iron(III) hydroxide oxide x H_2O; dimethicone; macrogol 400; titanium dioxide; hypromellose.

additionally for **Concor 10 mg**: Iron(III) oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life for PVC/aluminium blister
5 years.

Shelf-life for aluminium/aluminium blister
3 years.

The medicinal product is not to be used after the expiry date.

6.4 Special precautions for storage

Storage condition for PVC/alu blister
Do not store above 30 °C.

Storage condition for alu/alu blister
No special storage conditions required for this medicinal product.

6.5 Nature and contents of container

Concor 5 mg in PVC/aluminium blister:
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
Hospital pack with 30 film-coated tablets
Hospital pack with 100 film-coated tablets
Hospital pack with 250 film-coated tablets
Hospital pack with 300 (10 x 30) film-coated tablets

Concor 10 mg in PVC/aluminium blister:
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
Hospital pack with 30 film-coated tablets
Hospital pack with 250 film-coated tablets
Hospital pack with 300 (10 x 30) film-coated tablets

Concor 5 mg in aluminium/aluminium blister:
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

Concor 10 mg in aluminium/aluminium blister:
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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E-mail: Medwiss.Service@merckgroup.com

8. MARKETING AUTHORISATION NUMBER(S)

Concor 5 mg 6849.00.00
Concor 10 mg 6849.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Concor 5 mg: 28.01.1986 / 14.08.1990 / 14.09.1999 / 10.12.2004
Concor 10 mg: 28.01.1986 / 14.08.1990 / 14.09.1999 / 10.12.2004

10. DATE OF REVISION OF THE TEXT

February 2022

11. LEGAL CATEGORY

Medicinal product subject to medical prescription.