Summary of Product Characteristics

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 complete list of excipients see section 6.1.

3. Dosage form

Film-coated tablets

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

Tablets can be divided into equal halves.

4. Clinical data

4.1 Therapeutic indications

- Hypertension
- Coronary heart disease (angina pectoris)

4.2 Posology and method of administration

Posology

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

Hypertension
The recommended dosage is 5 mg bisoprolol fumarate once daily.
In 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 increase of dosage 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 increase of dosage 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 no dosage adjustment is normally 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.
There is only limited experience with the use of bisoprolol in dialysis patients. There are no indications of the necessity to alter the dose regimen.

Elderly people
No dose adjustment is required in elderly patients.

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

Method of administration

The film-coated tablets are to be swallowed whole with some liquid and not to be chewed in the morning before, during or after breakfast.

Duration of therapy

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

Concor therapy should not be stopped abruptly, particularly not 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 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 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 special precautions for use

Concor therapy should not be stopped abruptly, particularly not in patients with coronary heart disease, because this may lead to transitional worsening of heart condition (see section 4.2).

Concor must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Concor must 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
- 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 nonselectivebeta-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 bronchial asthma or other chronic obstructive pulmonary dysfunction that may be associated with symptoms, concomitant bronchodilating therapy is indicated. Occasionally an increase of airway resistance may occur in asthma patients, requiring a higher β_2-sympathomimetic dose.

General anaesthesia
In patients receiving general anaesthesia, beta-blockers reduce the risk of arrhythmia and myocardial ischemia during induction of anaesthesia, intubation, and postoperatively. It is currently recommended that maintenance of beta-blockade 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, and attenuation of reflex tachycardia, and decreased reflex ability to compensate for blood loss. If discontinuation of beta-blocker therapy prior to surgery is necessary, this should be done gradually and completed about 48 hours before anaesthesia.

Patients with a history of psoriasis should only be prescribed beta-blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

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

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

The use of Concor may lead to positive results in doping tests.

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 atrio-ventricular 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 antihypertensives may lead to deterioration of heart failure due to reduction of the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilatation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation may increase the risk of rebound hypertension.

Concomitant administration with the following drugs only with caution:

Class I antiarrhythmics (e.g. quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone): Effect on atrio-ventricular conduction time and negative inotropic effect may be increased.

Calcium antagonists of the dihydropyridine type (e.g. nifedipine): Concomitant administration may increase the risk of hypotension and impairment of ventricular pump function in patients with heart failure cannot be excluded.

Class III antiarrhythmics (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

Parasympathomimetics: Combination therapy may increase the atrio-ventricular conduction time and the risk of bradycardia.

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

Insulin and oral antidiabetic agents: Increase of blood sugar lowering effect. Blockade of betaadrenoceptors 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 atrio-ventricular conduction time.

Non-steroidal antiphlogistics (NSAIDs): decreased blood pressure lowering effect.
β-sympathomimetics (e.g. dobutamine, orciprenaline): Combination with bisoprolol may reduce the effect of both agents. Higher doses of adrenaline may be necessary for treatment of allergic reactions.

Sympathomimetics that activate α- and β-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 antihypertensives: Increased hypotensive effect.

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

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

The pharmacological activity of bisoprolol may have negative effects on pregnancy and/or the foetus/newborn infant.

In general, beta-blockers reduce placental perfusion possibly leading to intra-uterine growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g.

hypoglycaemia and bradycardia) may occur in the foetus and the newborn infant. If treatment with a beta-blocker is necessary, β_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 newborn infant 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 drug 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
Frequency not known: cannot be estimated from the available data

Investigations	
Rare	increased triglycerides, increased liver enzymes (ALAT, ASAT)
Cardiac disorders,	
Uncommon	bradycardia, AV-conduction disturbances, worsening of pre-existing heart failure
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 (itching, flush, rash)
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	sensation of cold or numb extremities
Uncommon	hypotension
General disorders and administration site conditions	
Common	tiredness*
Uncommon	asthenia
Hepatobiliary disorders	
Rare	hepatitis
Reproductive system and breast disorders	
Rare	potency disorders
Psychiatric disorders	
Uncommon	depression, sleep disorders
Rare	nightmares, hallucinations

*These symptoms occur especially 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 to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

a) Symptoms of intoxication

The most common signs of overdose with a beta-blocker are bradycardia, hypotension, bronchospasm, acute heart insufficiency 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 but available 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, $ß_2$-sympathomimetics 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 having neither intrinsic stimulating nor relevant membrane-stabilising activity. It shows only low affinity to the $beta_2$-receptor 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 negatively 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 suppresses the response to sympathoadrenergic activity by blocking cardiac beta$_1$-receptors. This causes slowing of the heart beat and decreasing contractility thus leading to reduced mycocardial oxygen consumption. The latter represents the desired effect in patients with angina pectoris and underlying coronary heart disease.

5.2 Pharmacokinetic properties

Absorption

More than 90% of an oral dose of bisoprolol is absorbed 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%.

Distribution

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

Metabolism and elimination

Bisoprolol is cleared from the body by two equally effective routes with 50% being metabolised by the liver to inactive metabolites which are then excreted by the kidneys and 50% being 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 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 5.1).

Linearity

The pharmacokinetics of bisoprolol are linear and independent of age.

5.3 Preclinical safety data

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

Reproduction

Reproduction toxicity studies with bisoprolol revealed no adverse effect on fertility or reproductive behaviour.
Like other beta-blockers, high doses of bisoprolol caused 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.

6. Pharmaceutical particulars

6.1 List of excipients

Concor 5 mg / 10 mg film-coated tablets

Tablet core: Colloidal anhydrous silica; 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.

In the **Concor 10 mg** additionally: Iron(III) oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

The medicinal product remains stable for 5 years.

The drug is not to be used after the expiry date.

6.4 Special precautions for storage

Do not store above 30 °C.

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

6.6 Special precautions for disposal

No special requirements for disposal.

7. Marketing authorisation holder

Merck Serono GmbH
Alsfelder Straße 17
D-64289 Darmstadt

Toll-free service-number:
Phone: 0800 42 88 373
Fax: +49-(0)6151 - 6285-816
E-mail: medizinpartner@merckserono.de

8. Marketing authorisation numbers

Concor 5 mg 6849.00.00
Concor 10 mg 6849.01.00

9. Date of marketing authorisation / renewal of marketing 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

June 2018

11. Legal category

Medicinal product subject to medical prescription.