



# Concor® 5

# Concor® 10

## Active ingredient: bisoprolol fumarate

### Composition

Each film-coated tablet contains 5 mg or 10 mg bisoprolol fumarate as active ingredient.

#### Excipients:

**Tablet core:** Silica, colloidal anhydrous; magnesium stearate, crospovidone, microcrystalline cellulose, maize starch, calcium hydrogen phosphate, anhydrous.

**Film coating:** Iron oxide yellow, dimethicone, macrogol 400, titanium dioxide, hypromellose.

Concor 10: All the above excipients include additional Iron oxide red.

### Properties

#### Pharmacodynamics

Bisoprolol fumarate, the active ingredient of Concor, is a beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows very 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 fumarate 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.

#### Pharmacokinetics

**Absorption.** Bisoprolol fumarate is almost completely (>90%) absorbed from the gastrointestinal tract and, because of its small first pass metabolism of approximately 10%, has an bioavailability of approximately 90% after oral administration. The bioavailability is not affected by food intake. Bisoprolol fumarate shows linear kinetics and the plasma concentrations are proportional to the administered dose over the dose range 5 to 20 mg. Peak plasma concentrations occur within 2-3 hours.

**Distribution.** Bisoprolol fumarate is extensively distributed. The volume of distribution is 3.5 l/kg. Binding to plasma proteins is approximately 30%.

**Metabolism.** Bisoprolol fumarate is metabolised via oxidative pathways with no subsequent conjugation. All metabolites, being very polar, are renally eliminated. The major metabolites in human plasma and urine were found to be without pharmacological activity. *In vitro* data from studies in human liver microsomes show that bisoprolol fumarate is primarily metabolised via CYP3A4 (~95%) with CYP2D6 having only a minor role.

**Elimination.** The clearance of bisoprolol fumarate is 'balanced' between renal elimination of the unchanged molecule (~50%) and hepatic metabolism (~50%) to metabolites which are also renally excreted. The total clearance of bisoprolol fumarate is approximately 15 l/h. Bisoprolol fumarate has an elimination half-life of 10-12 hours.

### Indication

- Treatment of high blood pressure (hypertension)
- Treatment of coronary heart disease (angina pectoris)
- Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction ≤ 35%, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

### Dosage and Administration

#### Treatment of hypertension or angina pectoris

In all cases the dose regimen is adjusted individually by your doctor, in particular according to the pulse rate and therapeutic success.

The usual initial dose 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 bisoprolol fumarate once daily.

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

#### Treatment of stable chronic moderate to severe heart failure

The initiation of treatment of stable chronic heart failure with Concor necessitates a special titration phase and requires regular monitoring by the doctor.

Preconditions for treatment with bisoprolol fumarate are:

- stable chronic heart failure without acute failure during the past six weeks,
- mainly unchanged basic therapy during the past two weeks,
- treatment at optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic, and optionally cardiac glycosides.

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 fumarate 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<sup>st</sup> week: 1.25 mg bisoprolol fumarate once daily

2<sup>nd</sup> week: 2.5 mg bisoprolol fumarate once daily

3<sup>rd</sup> week: 3.75 mg bisoprolol fumarate once daily

4<sup>th</sup> – 7<sup>th</sup> week: 5 mg bisoprolol fumarate once daily

8<sup>th</sup> –11<sup>th</sup> week: 7.5 mg bisoprolol fumarate once daily

12<sup>th</sup> week and beyond: 10 mg bisoprolol fumarate once daily as maintenance treatment

The treatment of stable chronic heart failure must be stated with a lower dose. The maximum recommended dose is 10 mg bisoprolol fumarate once daily.

Patients should be titrated to and maintained at this dose unless prevented by adverse effects.

After initiation of treatment with 1.25 mg bisoprolol fumarate, the patient should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure).

During the titration phase or thereafter, transient worsening of heart failure, fluid retention, hypotension or bradycardia may occur. In this case it is recommended first to reduce the dose of bisoprolol fumarate. Bisoprolol fumarate should be discontinued only if clearly necessary, but its reintroduction and/or uptitration should always be considered when the patient becomes stable again.

#### Duration of treatment for all indications

Treatment with Concor 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 heart condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. If discontinuation is necessary, the daily dose is gradually decreased.

### Special populations

#### Renal or hepatic impairment:

- **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 impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic impairment a daily dose of 10 mg bisoprolol fumarate must not be exceeded.
- **Treatment of stable chronic heart failure:** There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and concomitant hepatic or renal impairment. Titration of the dose in these populations must therefore be made with particular caution.

#### Elderly:

No dosage adjustment is required.

### Administration

Concor tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

### Contraindications

Concor must not be used in patients with:

- acute heart failure or during episodes of heart failure decompensation requiring intravenous therapy with substances increasing the contractility of the heart,
- shock induced by disorders of cardiac function (cardiogenic shock),
- severe disturbances of atrioventricular conduction (second or third degree AV block) without a pacemaker,
- sick sinus syndrome,
- sinoatrial block,
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma,
- severe forms of peripheral arterial occlusive disease or Raynaud's syndrome,
- untreated tumours of the adrenal gland (phaeochromocytoma),
- metabolic acidosis,
- hypersensitivity to bisoprolol fumarate or to any of the excipients (see Composition).

### Special warnings and precautions

The following section describes when Concor must be used with special caution:

- diabetes mellitus with extremely fluctuating blood glucose levels: symptoms of markedly reduced blood glucose (hypoglycaemia) such as tachycardia, palpitations or sweating can be masked,
- strict fasting,
- ongoing desensitisation therapy,
- mild disturbances of atrioventricular conduction (first degree AV block),
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol fumarate is administered to patients with Prinzmetal's angina. Utmost caution must be exercised.
- peripheral arterial occlusive disease (aggravation of symptoms may occur especially when starting therapy),
- patients with psoriasis or with a personal history of psoriasis

**Respiratory system:** 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 avoid 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 symptomatic 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.

**Allergic reactions:** Beta-blockers, including Concor, may increase the sensitivity to allergens and the severity of anaphylactic reactions because the adrenergic counterregulation under beta-blockade may be alleviated. Treatment with adrenaline may not always yield the expected therapeutic effect.

**General anaesthesia:** In patients undergoing general anaesthesia the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw Concor before surgery, this should be done gradually and completed about 48 hours prior to anaesthesia.

**Phaeochromocytoma:** In patients with a tumour of the adrenal gland (phaeochromocytoma) Concor may only be administered after previous alpha-receptor blockade.

**Thyrototoxicosis:** Under treatment with Concor the symptoms of a thyroid hyperfunction (thyrototoxicosis) may be masked.

### Special populations

So far no sufficient therapeutic experience is available in patients with heart failure and concomitant insulin dependent type I diabetes mellitus, severely impaired kidney function, severely impaired hepatic function, restrictive cardiomyopathy, congenital heart diseases or haemodynamically relevant organic valvular heart disease. No sufficient therapeutic experience is available in patients with heart failure and myocardial infarction within the last 3 months.

There is insufficient experience with bisoprolol fumarate in children, therefore the use of Concor cannot be recommended for children.

### Effects on the ability to drive and use machines

In a study with patients suffering from coronary heart disease bisoprolol fumarate did not affect the driving performance of the patients. However, depending on the individual patients response to treatment an effect on the

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

### Pregnancy and lactation

During pregnancy Concor is only recommended following careful assessment of benefit-to-risk ratio by the doctor. In general, beta-blockers reduce placental blood flow and may affect the development of the unborn child. Placental and uterine blood flow as well as the growth of the unborn child must be monitored and, in case of harmful effects on pregnancy or the foetus, alternative therapeutic measures considered.

The newborn infant must be monitored closely after delivery. Symptoms of reduced blood glucose and slowed pulse rate generally may occur within the first 3 days of life.

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

### Adverse effects

The adverse effects described below are sorted according to system organ classes. Frequencies are classified as follows:

Very common (affects more than 1 person in 10)

Common (affects less than 1 person in 10)

Uncommon (affects less than 1 person in 100)

Rare (affects less than 1 person in 1,000)

Very rare (affects less than 1 person in 10,000)

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; bradycardia (in patients with hypertension or angina pectoris); worsening of pre-existing heart failure (in patients with hypertension or angina pectoris)

#### • Nervous system disorders

Common: dizziness\*, headache\*

#### • 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

Frequency not known: syncope

#### • 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: erectile dysfunction

#### • Psychiatric disorders

Uncommon: depression, sleep disorder

Rare: nightmare, hallucination

\*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.

Tell your doctor if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly.

### Interactions

The effect and tolerability of medicines can be influenced by simultaneous intake of other medication. Such interactions can also occur if a short time has elapsed since the use of the other medication. Tell your doctor if you are taking any other medicine – even those not prescribed to you by a doctor.

### Combinations not recommended

#### Treatment of stable chronic heart failure

Class-I antiarrhythmic medicines (e.g. quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone) may increase the depressant effect of Concor on atrio-ventricular impulse conduction and the contractility of the heart.

#### All indications

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type may lead to reduced contractility of the heart muscle and delayed atrio-ventricular impulse conduction when used concomitantly with Concor. Especially intravenous administration of verapamil in patients on B-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting blood pressure-lowering medicines (such as clonidine, methyl dopa, moxonidine, rilmenidine) may lead to a reduction of heart rate and cardiac output, as well as to vasodilation due to a decrease in the central sympathetic tonus. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

### Combinations to be used with caution

#### Treatment of hypertension or coronary heart disease (angina pectoris)

Class-I antiarrhythmic medicines (e.g. quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone) may increase the depressant effect of Concor on atrio-ventricular impulse conduction and the contractility of the heart.

#### All indications

Calcium antagonists of the dihydropyridine type (e.g. nifedipine, felodipine, amlodipine) may increase the risk of hypotension when used concomitantly with Concor. An increased risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic medicines (e.g. amiodarone) may increase the inhibitory effect of Concor on atrio-ventricular impulse conduction.

Topical B-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of Concor.

Parasympathomimetic medicines may increase the inhibitory effect on atrio-ventricular impulse conduction and the risk of bradycardia when used concomitantly with Concor.

The blood sugar lowering effect of insulin or oral antidiabetic medicines may be increased. Warning signs of reduced blood glucose (hypoglycaemia) – especially accelerated heart rate (tachycardia)– may be masked or suppressed.

Such interactions are considered to be more likely with nonselective B-blockers.

Anaesthetic agents may increase the risk of cardiodepressive actions of Concor, leading to hypotension (for further information on general anaesthesia see also section special warnings and precautions).

Cardiac glycosides (digitalis) may lead to an increase in impulse conduction time and thus reduction in heart rate when used concomitantly with Concor.

Non-steroidal anti-inflammatory medicines (NSAIDs) may reduce the blood pressure-lowering effect of Concor.

B-Sympathomimetics (e.g. isoprenaline, dobutamine) used in combination with Concor may lead to a reduced effect of both agents.

A combination of Concor with sympathomimetics that activate both B- and α-adrenoceptors (e.g. noradrenaline, adrenaline) may intensify the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase. Such interactions are considered to be more likely with nonselective B-blockers.

Antihypertensive agents as well as other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the blood pressure lowering effect of Concor.

### Combinations to be considered

Mefloquine may increase the risk of decelerating the heart rate (bradycardia), if used in combination with Concor.

Monoamine oxidase inhibitors (except MAO-B inhibitors) may enhance the hypotensive effect of the beta-blockers. Concomitant use may also be a risk for hypertensive crisis.

### Overdose

The most frequent signs of Concor overdose include slow heart rate (bradycardia), marked drop in blood pressure, acute heart failure, hypoglycaemia and bronchospasm.

In the case of suspected Concor overdose please inform your doctor immediately. The effect of overdose may vary from one person to the next and patients with heart failure are probably very sensitive.

Depending on the degree of overdose your doctor can then decide which measures to take.

In general, if overdose occurs, bisoprolol fumarate treatment is stopped and supportive and symptomatic treatment is provided. Limited data suggest that bisoprolol fumarate is hardly dialysable.

### Storage and Stability

Do not store above 30°C.

Do not use after the expiry date.

### Keep medicines out of the reach of children.

### Presentations

**Concor 5:** blister with box pack

**Concor 10:** blister with box pack

### Date of Information

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### Merck Healthcare KGaA

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