Concor® 2.5 mg film coated tablet

Active ingredient: bisoprolol fumarate

Composition
Each film-coated tablet contains 2.5 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: Dimethicone, macrogol 400, titanium dioxide, hypromellose

Product Description
White, heart-shaped, biconvex film-coated tablet, scored on both sides

Route of Administration
Oral

Properties
Pharmacodynamics
Bisoprolol, 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 tothe 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.

Pharmacokinetics
Absorption. Bisoprolol is almost completely (>90%) absorbed from the gastrointestinal tract and, because of its small first pass metabolism of approximately 10%, has a bioavailability of approximately 90% after oral administration. The bioavailability is not affected by food intake. Bisoprolol 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 is extensively distributed. The volume of distribution is 3.5 l/kg. Binding to plasma proteins is approximately 30%.

Metabolism. Bisoprolol 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 is primarily metabolised via CYP3A4 (~95%) with CYP2D6 having only a minor role.

Elimination. The clearance of bisoprolol 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 is approximately 15 l/h. Bisoprolol has an elimination half-life of 10-12 hours.

Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

Indication

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

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,
- slowed heart rate, causing symptoms (symptomatic bradycardia),
- decreased blood pressure, causing symptoms (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 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),
- disturbed blood flow in the coronary vessels due to vasospasms (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.
- 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 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 symptomatic chronic obstructive pulmonary diseases concomitant bronchodilator therapy is indicated.
An increase in airway resistance may occasionally occur in patients with asthma, requiring a higher dose of beta2–sympathomimetics.

Allergic reactions: Beta-blockers, including Concor, may increase the sensitivity to allergens and the severity of anaphylactic reactions because the adrenergic counter regulation 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.

Thyrotoxicosis: Under treatment with Concor the symptoms of a thyroid hyperfunction (thyrotoxicosis) may be masked.

Special populations
So far, no sufficient therapeutic experience is available for Concor 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 either in patients with heart failure and myocardial infarction within the last 3 months.
There is insufficient experience with bisoprolol 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 did not affect the driving performance of the patients. However, depending on the individual patient response to treatment, 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 in human breast milk or the safety of bisoprolol 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
Common: worsening of pre-existing heart failure
Uncommon: AV-conduction disturbances

- *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, fatigue

- *Hepatobiliary disorders*

Rare: hepatitis

- *Reproductive system and breast disorders*

Rare: erectile dysfunction

- *Psychiatric disorders*

Uncommon: depression, sleep disorders
Rare: nightmares, hallucinations

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.

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 atrioventricular impulse conduction when used concomitantly with Concor. Especially intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting blood pressure-lowering medicines (such as clonidine, methyldopa, moxonodine, 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
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 cannotbe excluded.

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

Topical beta-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 beta-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.

β-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 β - 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 beta-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.

Dosage and Administration
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.

1st week	: 1.25 mg bisoprolol fumarate (½ tablet Concor 2.5) once daily
2nd week	: 2.5 mg bisoprolol fumarate (1 tablet Concor 2.5) once daily
3rd week	: 3.75 mg bisoprolol fumarate (1½ tablets Concor 2.5) once daily
4th – 7th week	: 5 mg bisoprolol fumarate once daily *
8th –11th week	: 7.5 mg bisoprolol fumarate once daily *
12th week and beyond	: 10 mg bisoprolol fumarate once daily as maintenance treatment *

* Concor 2.5 mg is suitable for initial treatment of stable chronic heart failure.
Higher strengths are available for maintenance treatment.

The maximum recommended dose is 10 mg fumarate once daily.

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

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 up-titration of bisoprolol should always be considered when the patient becomes stable again.

Duration of treatment
Treatment with Concor is generally a long-term therapy.
The treatment may be interrupted if necessary and reintroduced as appropriate.

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:

There is no information regarding pharmacokinetics of bisoprolol 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.

Children:

There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Administration

Concor tablets are taken in the morning and can be taken with food. They are swallowedwith some liquid and not to be chewed.

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 treatment is stopped and supportive and symptomatic treatment is provided. Limited data suggest that bisoprolol 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.

Shelf Life

3 years

Presentations

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

Pack sizes: 28, 56 and 100 tablets

Not all containers or pack sizes may be registered or marketed.

Name and Address of Manufacturer

Merck Healthcare KGaA
Frankfurter Strasse 250,
64293 Darmstadt, Germany

Product Registration Holder
Merck Sdn Bhd (178145-V)
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