# Prescribing Information

## BISOPROLOL FUMARATE TABLETS USP
## CONCOR ® 5/10

Active ingredient: Bisoprolol Fumarate

### Composition
### Concor 5:

Each film-coated tablet contains:
Bisoprolol fumarate IP.....5 mg
Excipients.....q.s.
Colours used: Ferric Oxide USPNF
(Yellow) & Titanium Dioxide IP


### Concor 10:

Each film-coated tablet contains:
Bisoprolol fumarate IP.....10 mg
Excipients.....q.s.
Colours used: Ferric Oxide USPNF (Yellow),
Ferric Oxide USPNF (Red) & Titanium Dioxide IP


**Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only**

### Indications

- Treatment of hypertension.
- Treatment of coronary heart disease (angina pectoris).
- Treatment of stable chronic heart failure.

### Dosage and Administration

**Treatment of hypertension or angina pectoris**

- The usual initial dose is 5 mg bisoprolol fumarate (1 tablet of Concor 5) once daily. If necessary, the dose may be increased to 10 mg bisoprolol fumarate (1 tablet of Concor 10) 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 heart failure**

- Standard treatment of CHF consists of an ACE inhibitor (or an ARB 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 recommended starting dose is 1.25 mg* bisoprolol fumarate once daily depending on individual tolerance the dose is stepwise increased to 2.5 mg*, 3.75 mg*, 5 mg, 7.5 mg, and 10 mg bisoprolol fumarate once daily in intervals of two weeks or longer.
- If a dose increase is not well tolerated treatment may be maintained at a lower dose.
- The treatment of stable chronic heart failure with bisoprolol must be started with a gradual titration according to the steps described below. During this titration phase, dose increase is dependent on how well the patient tolerates the current dose.

(* Concor 5 and Concor 10 are not suited for initial treatment; there are strengths of bisoprolol tablets with lower dose available)

- The maximum recommended dose is 10 mg bisoprolol fumarate once daily.
- Close monitoring of vital signs (blood pressure, heart rate) and symptoms of worsening heart failure is recommended during the titration phase.

**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 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 ischemic 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 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 experience with bisoprolol in children, therefore its use cannot be recommended for children.**

**Administration**
Concor tablets are taken in the morning with or without food. They are swallowed with 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.
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.
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.

**Contraindications**
Concor must not be used in patients with:
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy,
- 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.

**Special warnings and precautions**
- Concor must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.
- Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.
- There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:
- NYHA class II heart failure
- Insulin-dependent diabetes mellitus (type I)
- Impaired renal function (serum creatinine ≥ 300 micromo/l)
- Impaired liver function

- Patients older than 80 years
- Restrictive cardiomyopathy
- Congenital heart disease
- Haemodynamically significant organic valvular disease
- Myocardial infarction within 3 months
- 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, as with other beta blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect
- Mild disturbances of atrioventricular conduction (first degree AV block); 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. Utmost caution must be exercised
- Disturbed blood flow in the coronary vessels due to vasospasms (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 should only be given beta blockers (e.g. bisoprolol) after a careful balancing of benefits against risks.

*Respiratory system:* 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.
Although cardio-selective (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 chronic obstructive pulmonary diseases, which may cause symptoms, concomitant Broncho-dilating 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 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 blockage.
*Thyrotoxicosis:* Under treatment with Concor the symptoms of a thyroid hyperfunction (thyrotoxicosis) may be masked.

Special populations
There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:
- NYHA class II heart failure
- Insulin-dependent diabetes mellitus (type I)
- Impaired renal function (serum creatinine ≥ 300 micromol/l)
- Impaired liver function

- Patients older than 80 years
- Restrictive cardiomyopathy
- Congenital heart disease
- Haemodynamically significant organic valvular disease
- Myocardial infarction within 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's 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 in human breast milk or the safety of bisoprolol exposure in infants. Therefore, administration of Concor is not recommended during breastfeeding.

**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)
Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

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 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**

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. Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

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 time may be potentiated.

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

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. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia. 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 cardio-depressive actions of Concor, leading to hypotension. Attenuation of the reflex tachycardia and increase of the risk of 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.

Beta-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 beta- and alpha- adrenoceptors (e.g. noradrenaline, adrenaline) may intensify the alpha-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.
Mono-amino oxidase inhibitors (except MAO-B inhibitors) may enhance the hypotensive effect of the beta blockers. Concomitant use may also be risk for hypertensive crisis.
Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug metabolising enzymes. Normally no dosage adjustment is necessary.
Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

**Pregnancy:**
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.
**Lactation:** Breastfeeding is not recommended during administration of Concor.

**Adverse effects**
The adverse effects described below are sorted according to system organ classes. Frequencies are classified as follows:
Very common (≥ 10%) common (≥ 1% and < 10%)
uncommon (≥ 0.1% and < 1%)
rare (≥ 0.01% and< 0.1%) very rare (< 0.01%)).

Frequency not known (can not 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 (fainting)
- *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

  *Applies only to patients with hypertension or angina pectoris:*

  *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.

**Shelf Life:** Please refer Blister or Carton.

**Storage and Stability**

Store at temperature not more than 25°C, Protect from light. Do not use after the expiry date.
Keep medicines out of the reach of children.

**Dosage:** As directed by Physician.

**Presentations**

Concor 5: Packs of 3 strips of 10 tablets each.
Concor 10: Packs of 3 strips of 10 tablets each.

For further information Please write to:
Merck Specialities Private Limited, Godrej One, 8th Floor, Pirojshanagar, Eastern Express Highway, Vikhroli (East), Mumbai – 400 079, India.
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