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

Concor 5 mg: Each tablet contains 5 mg bisoprolol fumarate.
Concor 10 mg: Each tablet contains 10 mg bisoprolol fumarate.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

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

The tablet can be divided into two equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension and angina pectoris.

4.2 Posology and method of administration

Adults
For both indications the normal dosage is 1 tablet (5-10 mg) once daily as a single dose. If 5 mg is not given necessary effect, the dose may be increased to 10 mg once daily or very rarely to 20 mg once daily**.**

The maximum recommended dose is 20 mg once daily**.**

In all cases the dosage is adjusted individually, in order to avoid bradycardia.

In hypertension, Concor could be combined with diuretics if necessary effect is not achieved.

Treatment with bisoprolol is generally a long-term therapy.
Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly since this might lead to a transitory worsening of angina pectoris with risk of heart attack. Gradual reduction of the dosage for 1-2 weeks is recommended.
If it is thought necessary to withdraw Concor before surgery, this should be done gradually and completed about 48 hours before operation except in certain cases, for example thyrotoxicosis and phaeochromocytoma.

<u>Administration</u>

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

Special populations

Renal or liver impairment
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 liver function disorders it is recommended that a daily dose of 10 mg bisoprolol fumarate is not exceeded. Experience with the use of bisoprolol in renal dialysis patients is limited; however, there is no evidence that the dosage regimen needs to be altered.

Elderly
No dosage adjustment is required.

Children
There no experience with bisoprolol in children, therefore its use cannot be recommended for children.

4.3 Contraindications

Bisoprolol is contra-indicated in patients with

- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy,
- cardiogenic shock,
- AV block of second or third degree (without a pacemaker),
- sick sinus syndrome,
- sinoatrial block,
- bradycardia with less than 60 beats/min before start of the treatment,
- hypotension (systolic bloodpressure less than 100 mm Hg),
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome,
- untreated phaeochromocytoma (see section 4.4),
- metabolic acidosis.
- hypersensitivity to bisoprolol or to any of the excipients.

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in patients with:

- hypertension or angina pectoris and accompanying heart failure.
- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked,
- strict fasting,
- ongoing desensitisation therapy.
- AV block of first degree,
- 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. Intensification of complaints may occur especially when starting therapy.

In patients undergoing the general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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 chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of $beta_2$-stimulants may have to be increased.

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.

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

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

Under treatment with bisoprolol the symptoms of a thyreotoxicosis may be masked.

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

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

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine):
Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). 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 such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

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

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

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs:
Intensification of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia (for example tachycardia).

Anaesthetic agents:
Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs):
NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine):
Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline):
Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered
Mefloquine:
Increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors):
Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

4.6 Pregnancy and lactation

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, β-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, β1-selective adrenoceptor blockers are preferable.
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
There are no data on the excretion of bisoprolol in human breast milk. Therefore, breastfeeding is not recommended during administration of Concor**.**

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 individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This is to be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter.

Very common (≥ 1/10)
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 available data)

Investigations
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT)

Cardiac disorders
Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure; bradycardia

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 (pruritus, flush, rash and angioedema)
Very rare: alopecia. β-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

General disorders
Common: fatigue
Uncommon: asthenia

Hepatobilary 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.

An increased level of antinuclear antibodies (ANA) have been noticed, but the clinical relevance of this is not clear.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649

4.9 Overdose

In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol.

If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07AB07

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

Bisoprolol has a negative inotropic and cronotropic effect.

Bisoprolol reaches its maximal effect 3-4 hours after oral administration.

The maximal antihypertensive effect of bisoprolol is generally reached after 2 weeks.

In acute administration, bisoprolol reduces the heart rate and stroke volume, thus reducing cardiac output. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.

The kinetics of bisoprolol are linear and independent of age.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concor 5 mg
Tablet core:
Silica, colloidal anhydrous;

Magnesium stearate;
Crospovidone;
Microcrystalline cellulose;
Maize starch;
Calcium hydrogen phosphate, anhydrous.

Film coating:
Iron oxide yellow (E172);
Dimethicone;
Macrogol;
Titanium dioxide (E171);
Hypromellose.

Concor 10 mg
Tablet core:
Silica, colloidal anhydrous;
Magnesium stearate;
Crospovidone;
Microcrystalline cellulose;
Maize starch;
Calcium hydrogen phosphate, anhydrous.

Film coating:
Iron oxide yellow (E172); Iron oxide red
Dimethicone;
Macrogol;
Titanium dioxide (E171);
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Blister pack of PVC film and cover by aluminium blister
5 mg: 30 tablets
10 mg: 30 tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck A.E. Hellas
41-45 Kifissias av. (Building B),
15123 Marousi, Athens

Greece

8. MARKETING AUTHORISATION NUMBER(S)

Concor 5 mg: 12863
Concor 10 mg: 21708

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Concor 5 mg:
Date of first authorization: **27/7/90**
Date of last renewal: 2/12/2011

Concor 10 mg:
Date of first authorization: **1/3/13**
Date of last renewal: 08/11/19

10. DATE OF REVISION OF THE TEXT

08/2022