1. NAME OF MEDICINAL PRODUCT

Concor® AMLO Tablet 5 mg/5 mg
Concor® AMLO Tablet 5 mg/10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concor® AMLO Tablet 5 mg/5 mg: 5.0 mg bisoprolol fumarate, 5.0 mg amlodipine (as 6.95 mg amlodipine besilate) per tablet.
Concor® AMLO Tablet 5 mg/10 mg: 5.0 mg bisoprolol fumarate, 10.0 mg amlodipine (as 13.9 mg amlodipine besilate) per tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Concor® AMLO Tablet 5 mg/ 5 mg: White or almost white, odourless, oblong, slightly convex tablets with score line on one side and with embossed MS on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Concor® AMLO Tablet 5 mg/ 10 mg: White or almost white, odourless, round, flat,bevel edged tablets with score line on one side and embossed MS on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Concor® AMLO is indicated for treatment of hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same doses level as in the combination, but as separate tablets.

4.2 Posology and method of administration

Concor® AMLO is indicated in patients whose blood pressure is adequately controlled with separately administered monocomponent preparations of the same doses as the recommended fixed dose combination.

Recommended daily dose is one tablet of the given strength.

Treatment must not be abruptly discontinued, as it may lead to temporary deterioration of clinical condition. Treatment must not be abruptly discontinued especially in case of patients suffering from ischaemic heart disease. Gradual decrease of the dose is recommended.

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Patients with hepatic impairment:
In case of hepatic impairment elimination of amlodipine may be elongated. Exact dosage recommendations concerning amlodipine have not been established, but the drug should therefore be administered with special caution in these patients (see section 4.4).

In case of severe hepatic impairment the daily dose of bisoprolol must not exceed 10mg.

Patients with renal impairment:
No dosage adjustment is required for patients with mild to moderate renal impairment.

Amlodipine is not dialyzable. Amlodipine should be administered with particular caution to patients undergoing dialysis (see section 4.4).

In case of severe renal impairment (creatinine clearance < 20ml/min) the daily dose of bisoprolol must not exceed 10mg.

Elderly patients:
The usual doses can be administered to elderly people; however, caution is advised when the dose is increased (see section 5.2).

Paediatric population:
The safety and efficacy of Concor® AMLO in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration
Concor® AMLO should be taken in the morning with or without food, without chewing it.

4.3 Contraindications
In connection with amlodipine:
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

In connection with bisoprolol:
- Acute heart failure or during episodes of heart failure requiring i.v. inotropic therapy
- Cardiogenic shock
- Second or third degree AV block (without a pacemaker)
- Sick sinus syndrome
- Sinoatrial block
- Bradycardia (heart rate less than 60 beats/min) prior to start of therapy
- Hypotension (systolic blood pressure < 100mmHg)

- Severe bronchial asthma
- Severe forms of peripheral arterial occlusive disease and severe forms of Raynaud's syndrome
- Untreated phaeochromocytoma (see section 4.4)
- Metabolic acidosis

In connection with Concor® AMLO:
- Hypersensitivity to amlodipine, dihydropyridine derivates, bisoprolol and/or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In connection with amlodipine:
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not associated with worsening of the heart failure.

Use in patients with impaired hepatic function
The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

Use in elderly patients
In the elderly increase of the dosage should take place with care (see section 5.2).

Use in renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

In connection with bisoprolol:
Especially in case of patients suffering from ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, as it may lead to temporary deterioration of heart disease (see section 4.2).

Bisoprolol should be administered with special caution in patients with hypertension or angina associated with heart failure.

Bisoprolol must be used with caution in:
- Diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked.

- Strict fasting/diet.
- Concomitant desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment may not always give the expected therapeutic effect.
- 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 is administered to patients with Prinzmetal's angina. Utmost caution must be exercised.
- Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy).
- 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.
- Under treatment with bisoprolol the symptoms of hyperthyreosis may be masked.
- In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockage.
- In patients undergoing general anaesthesia beta-blockage reduces the incidence of arrhythmias and myocardial ischemia during induction of anaesthesia and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockage be continued perioperatively. The anaesthetist must be aware of beta-blockage 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 anesthesia.
- Although cardioselective (beta 1) 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 AMLO 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 β2-stimulants may have to be increased.

4.5 Interactions with other medicinal products and other forms of interactions

In connection with amlodipine:

It has been safely administered with thiazide diuretics, β-blockers, long-acting nitrates, sublingual glyceryl trinitrate preparations, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs.

Effects of other medicinal products on amlodipine:

- CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate inhibitors of CYP3A4 (e.g. protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapramil or diltiazem) can be expected to increase the plasma concentrations of amlodipine to a clinically relevant extent.

- CYP3A4 inducers: Upon co-administration of known inducers f the CYP3A4, the plasma concentration of amlodipine may drop. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum)

In clinical interaction studies cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinectics of amlodipine.

Effect of amlodipine on other medicinal products:
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine: No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin: Combination with amlodipine may lead to an increase in simvastatin plasma level. Simvastatin doses of more than 20 mg daily are not recommended in patients treated with amlodipine.

In clinical interaction studies, amlodipine did not affect the pharmacokinectics of atorvastatin, digoxin, ethanol (alcohol), warfarin or cyclosporin.

There is no effect of amlodipine on laboratory parameters.

<u>In connection with bisoprolol:</u>
Combinations not recommended:
- *Calcium antagonists of verapramil type and to a lesser extent of diltiazem type:* Negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of verapramil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.
- *Centrally acting antihypertensive drugs* such as clonidine, methyldopa, moxonodine, rilmenidine: Concomitant use of centrally acting

antihypertensive drugs may lead to reduction of heart rate and cardiac output and vasodilation. Abrupt withdrawal of the drug may increase the risk of “rebound hypertension”.

Combinations to be used with special caution:
- *Calcium antagonists of the dihydropyridine type* such as nifedipine: Concomitant use may increase 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 I antiarrhythmic drugs* (e.g. disopyramide, quinidine, lidocaine, phenytoin, flecainide, propafenone): Effect on atrio-ventricular conduction time and negative inotropic effect may be potentiated.
- *Class III antiarrhythmic drugs* (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.
- *Parasympathomimetic drugs:* Concomitant use may increase atrio-ventricular conduction time and thus the risk of bradycardia.
- *Topical beta-blocker containing preparations* (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- *Insulin and oral antidiabetic drugs*: Intensification of blood sugar lowering effect. Blockage of beta-adrenoceptors may mask symptoms of hypoglycaemia.
- *Anaesthetic agents*: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see 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.
- *Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine):* Combination with bisoprolol may reduce the effect of both agents.
- *Sympathomimetics that activate both beta- and alpha-adrenoceptors* (e.g. norepinephrine, epinephrine): Combination with bisoprolol may unmask 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.
- *Concomitant use with antihypertensive agents as well as 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.
- *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.

4.6 Fertility, 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, spontaneous abortion and 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.

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans.

Concor® AMLO is not recommended during pregnancy unless clearly necessary. If treatment with Concor® AMLO is considered necessary, the uteroplacental blood flow and the foetal growth should be closely monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

It is not known whether bisoprolol is excreted in human milk. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Therefore, administration of Concor AMLO is not recommended during breast-feeding.

Fertility

No human data on fertility are known for the combination product. Reversible biochemical changes in spermatozoa have been reported in some patients treated by calcium channel blockers, however clinical data are insufficient regarding the potential effect of amlodipine on fertility.
Bisoprolol had no influence on fertility or on general reproduction performance in animal studies, while amlodipine showed in a published investigation adverse effects on male fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded.

This may occur mostly at the beginning of therapy, during changing therapy and during concomitant alcohol intake.

4.8 Undesirable effects

The undesirable effects observed in the course of using active ingredients separately are to be give according to the following frequency grouping:

Very common (≥ 1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10,000 to < 1/1000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from the available data)

In connection with amlodipine:
During placebo-controlled studies with patients suffering of hypotension and angina pectoris, most frequently reported adverse effects were as follow: headache, oedemas (especially ankle oedema), increased fatigue, somnolence, nausea, abdominal pain, flush, palpitation and dizziness.

In these clinical trials clinically significant laboratory abnormalities in relation with amlodipine have not been observed.

Blood and lymphatic system disorders:
Very rare: Leukopenia, thrombocytopenia

Immune system disorders:
Rare: Allergic reactions, mainly affecting the skin

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia

Psychiatric disorders:
Uncommon: Insomnia, mood changes (including anxiety), depression, sleep disorders
Rare: Nightmare, hallucinations, confusion

Nervous system disorders:
Common: Headache, dizziness, somnolence. These symptoms especially occur at the beginning of therapy. There are generally mild and often disappear within 1-2 weeks.
Uncommon: Hypoesthesia, paraesthesia, dysgeusia, tremor
Very rare: Peripheral neuropathy

Eye disorders:
Uncommon: Visual disturbance (including diplopia)
Rare: Decreased tear secretion (to be considered if the patient uses contact lenses)
Very rare: Conjunctivitis

Ear and labyrinth disorders:
Uncommon: Tinnitus
Rare: Hearing disorders

Cardiac disorders:
Common: Palpitations
Uncommon: Atrioventricular-conduction disturbances, worsening of pre-existing heart failure, bradycardia
Very rare: Myocardial infarction, arrhythmia

Vascular disorders:
Common: Flushing, feeling of coldness and numbness in the extremities
Uncommon: Hypotension, syncope
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, bronchospasm in patients with bronchial asthma or a history of obstructive pulmonary disease, rhinitis
Rare: Allergic rhinitis
Very rare: Cough

Gastrointestinal disorders:
Common: Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation, abdominal pain
Uncommon: Dyspepsia, dry mouth
Very rare: Gastritis, gingival hyperplasia, pancreatitis

Hepatobiliary disorders:
Rare: Hepatitis (in most cases with cholestasis)
Very rare: Jaundice (in most cases with cholestasis)

Skin and subcutaneous tissue disorders:
Uncommon: Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, exanthema
Very rare: Angio-oedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, psoriasis (psoriasis like skin disorders or aggravated psoriasis), photosensitivity
Frequency not known: Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders:
Uncommon: Arthralgia, myalgia, muscular weakness, muscle cramps, back pain
Very rare: Muscular hypertonia

Renal and urinary disorders:
Uncommon: Micturition disorder, nocturia, pollakiuria

Reproductive system and breast disorders:

Uncommon: Erectile dysfunction, gynaecomastia

General disorders:
Common: Oedema (e.g. ankle oedema), fatigue (especially at the beginning of therapy; generally mild and often disappear within 1-2 weeks)
Uncommon: Asthenia (especially at the beginning of therapy; generally mild and often disappear within 1-2 weeks), chest pain, pain, malaise

Investigations:
Uncommon: Weight increase, weight decrease
Rare: Increased triglycerides, increased liver enzymes (ALAT, ASAT)

4.9 Overdose

In connection with amlodipine:
In humans experience with intentional overdose is limited.

Symptoms
Available data suggest that gross overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment
Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, attention to circulating fluid volume and urine output, symptomatic treatment is needed.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockage.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In connection with bisoprolol:
Symptoms
The most common signs expected with overdosage of a β-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose with bisoprolol in hypertensive and/or ischemic heart disease patients have been reported: Bradycardia and/or

hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity and in reactions to one single high dose of bisoprolol, patients with heart disease are obviously more sensitive to the effects of bisoprolol.

Treatment:
If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialyzable.

Based on the expected pharmacological actions and recommendations are other β-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. Intravenous glucagon may be useful.

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

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

Bronchospasm: Bronchodilator therapy such as isoprenaline, β_2-sympathomimetic drugs and/or aminophylline.

Hypoglycemia: i.v. glucose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, and other antihypertensives.

ATC code: C07 FB 07

Mechanism of action of amlodipine:
Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle (slow channel blocker or calcium ion antagonist).

The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle causing reduction in peripheral vascular resistance.

The precise mechanism by which it relieves angina has not been fully determined, it may have the following two actions:

1) It dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload). Since it does not cause reflex tachycardia, myocardial energy consumption and oxygen requirement will be reduced.
2) By means of dilation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions it improves oxygen supply. By the above mechanism it increases myocardial oxygen delivery even in cases of coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic effects
In patients with hypertension, once daily dosing of provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of its administration.

In patients with angina, by once daily administration it increases total exercise time, time to angina onset, and time to significant ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablets consumption.

It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood sugar and serum uric acid and it was suitable for use in patients with asthma.

Mechanism of action of bisoprolol:
Bisoprolol is a potent, highly β_1-selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilising activity. It only shows low affinity to the β_2-receptor of the smooth muscles of bronchi and vessels as wells as to the β_2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β_2-mediated metabolic effects. Its β_1-selectivity extends beyond the therapeutic dose range. Bisoprolol has no explicit negative inotropic effect. Bisoprolol has its maximal effect 3-4 hours after oral administration.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

It usually exerts its maximal antihypertensive effect after 2 weeks.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Antihypertensive effect of beta-blockers is among others due to decrease of renin activity.

Pharmacodynamic effects of the combination product

This combination allows to increase the antihypertensive and anti-anginal efficacy by complementary mechanism of actions of the two active compounds: vasoselective effect of the calcium channel blocker amlodipine (decrease of peripheral resistance) and cardioselective beta-blocker bisoprolol (decrease of cardiac output).

5.2 Pharmacokinetic properties

Amlodipine

Absorption: After oral administration, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Its bioavailability is unaffected by food ingestion. Absolute bioavailability has been estimated to be between 64 and 80%.

Distribution: The volume of distribution is 21 l/kg. Steady state plasma concentration (5-15 ng/ml) is reached after 7-8 days of consecutive daily dosing. In vitro studies have shown that 93-98% of circulating amlodipine is bound to plasma proteins.

Metabolism and elimination: Amlodipine is extensively metabolised (approx. 90%) by the liver to inactive pyridine derivates. 10% of the parent compound and 60% of inactive metabolites excreted in the urine, 20-25 % with faeces. Decrease of plasma concentration shows biphasic characteristics. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Total clearance is 7ml/min/kg (in case of 60 kg-patient: 25 litre/hour). In elderly patients this value is 19 litre/hour.

Elderly patients

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group study (see section 4.4).

Patients with impaired renal function

Amlodipine is extensively metabolized into inactive metabolites. 10% of the parent compound is excreted unchanged in the urine. The changes in the plasma concentration of amlodipine are not related to the degree of renal impairment. These patients can be treated with a normal dosage of amlodipine. Amlodipine is not dialyzable.

Patients with impaired hepatic function

The half-life of amlodipine is prolonged in patients with impaired hepatic function.

Pharmacokinetic interaction studies

With concomitant use of amlodipine with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50% respectively. There is no data available regarding the effect of CYP3A4 inducers on amlodipine.

Bisoprolol:
Absorption: Bisoprolol is almost completely (>90%) absorbed from the gastrointestinal tract. Due to the very small first pass effect (approx. 10%), its absolute bioavailability is approximately 90% after oral administration.

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

Metabolism and elimination: Bisoprolol is excreted from the body by two routes ensuring equivalent elimination. 50% is metabolized 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 mild to moderate liver function impairment or renal insufficiency. Total clearance is approximately 15 litre/hour.

The elimination half-life in plasma is 10-12 hours.
The kinetics of bisoprolol are linear and independent of age.

Combination product
There has not been conducted any pharmacokinetic interaction study between the two compounds.
Even if such interaction exists, according to the results of bioequivalence study, the extent of this hypothetic interaction must be the same in case of taking Concor® AMLO tablets, than in cases of taking the two compounds separately at the same dose levels as in the combination.

5.3 Preclinical safety data

In connection with amlodipine:
Carcinogenesis:
Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose.

Mutagenesis:
Mutagenicity studies revealed no drug related effects at either the gene or chromosome level.

Fertility:
Standard fertility investigation revealed no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10mg/kg/day amlodipine (8 times the maximum recommended human dose of 10mg/day on a mg/m^2 basis). However, in a

published investigation in which male rates were treated with amlodipine besilate for 30 days at dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

In connection with bisoprolol:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. During reproduction toxicology tests bisoprolol had no influence on fertility or general reproduction ability.

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight increase) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) but was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Magnesium stearate
Sodium starch glycolate (type A)
Cellulose, microcrystalline

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30^{o}C. Store in the original container in order to protect from light.

6.5 Nature and contents of container

28, 30, 56, or 90 tablets in OPA/Al/PVC//Al blister and carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MANUFACTURER

EGIS Pharmaceuticals PLC
Bökényföldi út 118-120
1165 Budapest
Hungary

8. DATE OF REVISION OF TEXT

November 2022 (CCDS v9)