Professional Information

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

EMCOR 5/5 FDC

EMCOR 5/10 FDC

EMCOR 10/5 FDC

EMCOR 10/10 FDC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Emcor FDC 10+10: Each tablet contains 10 mg bisoprolol fumarate and 10 mg amlodipine (as 13.9 mg amlodipine besilate) as active ingredients.

Emcor FDC 10+5: Each tablet contains 10 mg bisoprolol fumarate and 5 mg amlodipine (as 6.95 mg amlodipine besilate) as active ingredients.

Emcor FDC 5+10: Each tablet contains 5 mg bisoprolol fumarate and 10 mg amlodipine (as 13.9 mg amlodipine besilate) as active ingredients.

Emcor FDC 5+5: Each tablet contains 5 mg bisoprolol fumarate and 5 mg amlodipine (as 6.95 mg amlodipine besilate) as active ingredients.

Sugar-free

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Emcor FDC 10+10: White or almost white, round slightly convex tablets with score line on one side and embossed MS on the other side.

Emcor FDC 10+5: White or almost white, oval shaped, slightly convex

tablets with score line on one side and embossed MS on the other side.

Emcor FDC 5+10: White or almost white, round, flat, bevel edged tablets with score line on one side and embossed MS on the other side.

Emcor FDC 5+5: White or almost white, 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Emcor FDC is indicated for the treatment of hypertension in patients whose blood pressure cannot be controlled by either bisoprolol or amlodipine monotherapy.

4.2 Posology and method of administration

Posology

Emcor FDC is indicated in patients whose blood pressure is adequately controlled with separately administered mono-component medicines of the same doses as the recommended fixed dose combination.

Emcor FDC is indicated in patients whose blood pressure is not adequately controlled with bisoprolol or amlodipine alone.

Treatment with **Emcor FDC** is started with the lowest dose of Bisoprolol/Amlodipine 5/5 mg for the first 6 weeks. After 6 weeks the dosage for patients with uncontrolled blood pressure may be increased to Bisoprolol/Amlodipine 5/10 mg or Bisoprolol/Amlodipine 10/5 mg according to tolerability.

After further 6 weeks the dosage for patients with uncontrolled blood pressure may be increased to Bisoprolol/Amlodipine 10/10 mg. For patients who are not tolerating their increased dose, their dose should be down titrated to their prior dose.

The recommended daily dose is one tablet of the given strength.

Treatment with **Emcor FDC** must not be stopped abruptly, since the abrupt withdrawal of bisoprolol may lead to a transitory worsening of clinical condition. Especially in case of patients with ischaemic heart disease treatment must not be discontinued suddenly. Gradual reduction of the daily dose is recommended, and patients should be advised to limit the extent of their physical activity during the period that **Emcor FDC** is being discontinued.

Elderly:

No dosage adjustment is required however, caution is advised when the dose is increased.

Paediatric patients:

There is no experience with **Emcor FDC** in the paediatric population, therefore its use cannot be recommended.

Renal impairment:

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

In case of severe renal impairment (creatinine clearance < 30 ml/min) the daily dose of the bisoprolol component of **Emcor FDC** must not exceed 10 mg.

Hepatic impairment:

In case of severe hepatic impairment, the daily dose of the bisoprolol component in **Emcor FDC** must not exceed 10 mg. Due to the amlodipine component in case of hepatic impairment special caution must be taken when **Emcor FDC** is administered.

Method of administration:

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

4.3 Contraindications

Emcor FDC is contra-indicated in patients with:

- Hypersensitivity to bisoprolol, amlodipine, dihydropyridine derivatives, or to any of the excipients of **Emcor FDC** listed in section 6.1
- Acute heart failure or during episodes of heart failure decompensation requiring intravenous inotropic therapy,
- Obstruction of the outflow tract of the left ventricle (e.g. high-grade aortic stenosis),
- Cardiogenic shock,
- 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 severe forms of Raynaud's syndrome,
- Untreated phaeochromocytoma,
- Metabolic acidosis.

4.4 Special warnings and precautions for use

Warnings:

Patients with heart failure:

Patients with heart failure should be treated with caution. An increased risk of a further deterioration of the ventricular pump function cannot be excluded. Especially in patients with ischaemic heart disease the cessation of therapy with **Emcor FDC** must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.

Patients with impaired hepatic function:

Caution is advised when **Emcor FDC** is administered in patients with impaired hepatic function, since the half-life of amlodipine is prolonged.

Due to the bisoprolol component, **Emcor FDC** must be used with caution in:

- Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked.
- Strict fasting.
- Ongoing desensitisation therapy. Bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine (adrenaline) treatment may not always yield 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.
- Peripheral arterial occlusive disease (aggravation of symptoms might happen especially when starting therapy).
- Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after carefully balancing of benefits against risks.
- Under treatment with **Emcor FDC** the symptoms of thyrotoxicosis may be masked.
- In patients with phaechromocytoma bisoprolol must not be administered until after alpha-receptor blockade (see section 4.3).
- In patients undergoing general anaesthesia beta-blockade reduces the incidence of dysrhythmias and myocardial ischemia during induction of anaesthesia and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued perioperatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicines, resulting in bradydysrhythmias, 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, these should be avoided in patients with obstructive airway diseases, unless there are compelling clinical reasons for their use.

Where such reasons exist, **Emcor FDC** may be used with caution.

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, broncho-dilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of β_2-stimulants may have to be increased.

Use in children:

Safety and efficacy have not been established.

Use in elderly:

In the elderly increase of the dosage should take place with care (see Section 5.2)

4.5 Interaction with other medicinal products and other forms of interaction

Interactions:

Combinations not recommended

Calcium antagonists of verapamil type and to a lesser extent of diltiazem type:
In combination with bisoprolol negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting antihypertensive medicines such as clonidine, methyldopa, moxonidine, rilmenidine: Concomitant use of centrally acting antihypertensive medicines with bisoprolol as in **Emcor FDC** may lead to reduction of heart rate and cardiac output and vasodilation. Abrupt withdrawal of the medicine may increase the risk of “rebound hypertension.

It is dangerous to administer **Emcor FDC** concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines. Such drug-drug interactions can have life-threatening consequences.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Combinations to be used with caution:

The metabolism of amlodipine takes place via the main pathway of CYP3A4 iso-enzymes of the Cytochrome P450 system.

CYP3A4 inhibitors:

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

CYP3A4 inducers:

Upon co-administration of known inducers of 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).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as the bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

***Simvastatin*:**

Combination with amlodipine may lead to an increase in simvastatin plasma level, and therefore increased the risk of myopathy. 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 pharmacokinetics of atorvastatin, digoxin or warfarin.

***Tacrolimus*:**

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of the 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.

Ciclosporin:

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

Class I antidysrhythmic medicines (e.g. disopyramide, quinidine, lidocaine, phenytoin, flecainide, propafenone):

In combination with bisoprolol the effect on atrio-ventricular conduction time and negative inotropic effect may be potentiated.

Class III antidysrhythmic medicines *(e.g. amiodarone):*

In combination with bisoprolol the effect on atrio-ventricular conduction time may be potentiated.

Parasympathomimetic medicines:

Concomitant use with bisoprolol may increase atrio-ventricular conduction time and thus the risk of bradycardia.

Topical beta-blocker containing preparations (e.g. eye drops for glaucoma treatment):

They may contribute to the systemic effects of bisoprolol.

Insulin and oral antidiabetic medicines:

In combination with bisoprolol intensification of blood sugar lowering effect may occur. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic medicines:

In combination with bisoprolol the reflex tachycardia may be attenuated and the risk of hypotension may be increased (for further information on general anaesthesia see section 4.4).

Digitalis glycosides:

Concomitant use with bisoprolol may lead to a reduction of heart rate, or an increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs may reduce the hypotensive effect of bisoprolol.

Beta-sympathomimetic medicines (e.g. isoprenaline, dobutamine):

Combination with bisoprolol may reduce the effect of both medicines.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine (noradrenaline), epinephrine (adrenaline)):
Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these medicines leading to blood pressure increase. Such interactions are considered to be more likely with nonselective beta-blockers.

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

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers (such as bisoprolol) are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect.

If a beta-blocker (such as bisoprolol) and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.

Combinations to be considered:

Mefloquine:
In combination with bisoprolol increased risk of bradycardia.

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

Ergotamine derivatives:

In combination with bisoprolol exacerbation of peripheral circulatory disturbances.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation:

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-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.

The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Emcor FDC is not recommended during pregnancy unless clearly necessary. If treatment with **Emcor FDC** 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.

Breastfeeding:

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 **Emcor FDC** is not recommended during breastfeeding.

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.

4.7 Effects on ability to drive and use machinery

Some adverse reactions to **Emcor FDC** (e.g. dizziness, headache, or fatigue) may affect the patient's ability to concentrate and react and may therefore constitute a risk in situations where these abilities are of special importance, e.g. driving or using machines. Patients should not drive until they know how treatment with **Emcor FDC** affects them.

4.8 Undesirable effects

Adverse reactions reported are listed below by system organ class and by frequency.

Frequencies are defined as:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10 000), very rare (< 1/10 000) and Frequency not known (cannot be estimated from the available data)

In connection with amlodipine

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Blood and lymphatic system disorders

Very rare	Leukopenia, thrombocytopenia

Immune system disorders

Very rare	Allergic reactions, mainly affecting the skin, angioedema

Metabolism and nutrition disorders

Very rare:	Hyperglycaemia

Psychiatric disorders

Uncommon:	Depression, mood changes (including anxiety), insomnia
Rare:	Confusion

Nervous system disorders

Common:	Somnolence, dizziness, headache (especially at the beginning of the treatment)
Uncommon:	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare:	Hypertonia, peripheral neuropathy

Eye disorders

Common:	Visual disturbances (including diplopia)

Ear and labyrinth disorders

Uncommon:	Tinnitus

Cardiac disorders

Common:	Palpitation
Uncommon:	Dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Very rare:	Myocardial infarction

Vascular disorders

Common:	Flushing
Uncommon:	Hypotension
Very rare:	Vasculitis

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea
Uncommon:	Cough, rhinitis

Gastrointestinal disorders

Common:	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
Uncommon:	Vomiting, dry mouth
Very rare:	Pancreatitis, gastritis, gingival hyperplasia

Hepatobiliary disorders

Very rare:	Hepatitis, jaundice, hepatic enzyme increased*

Skin and subcutaneous tissue disorders

Uncommon:	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
Very rare:	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Not known:	Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common:	Ankle swelling, muscle cramps

Uncommon: Arthralgia, myalgia, back pain

Renal and urinary disorders

Uncommon: Micturition disorder, nycturia, increased urinary frequency

Reproductive system and breast disorders

Uncommon: Erectile dysfunction, gynecomastia

General disorders and administration site conditions

Very common: Oedema

Common: Fatigue, asthenia

Uncommon: Chest pain, pain, malaise

Investigations

Uncommon: Weight increase, weight decrease

*In most cases with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

In connection with bisoprolol

Metabolism and nutrition disorders

Rare: Elevated triglyceride level

Psychiatric disorders

Uncommon: Depression, sleep disorders

Rare: Nightmares, hallucinations

Nervous system disorders

Common:	Dizziness**, headache**
Rare:	Syncope

Eye disorders

Rare:	Decreased tear secretion (it must be taken into consideration if the patient wears contact lenses)
Very rare:	Conjunctivitis

Ear and labyrinth disorders

Rare:	Hearing impairments

Cardiac disorders

Uncommon:	AV-conduction disorders, deterioration of pre-existing heart failure, bradycardia

Vascular disorders

Common:	Feeling of coldness and numbness in the extremities
Uncommon:	Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon:	Bronchospasm in patients with bronchial asthma or a history of obstructive pulmonary disease
Rare:	Allergic rhinitis

Gastrointestinal disorders

Common:	Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Hepatobiliary disorders

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Rare: Hypersensitivity reactions such as pruritus, flush, rash

Very rare: Alopecia. Beta-blockers can provoke or aggravate psoriasis or may cause psoriasis like skin disorder

Musculoskeletal and connective tissue disorders

Uncommon: Muscle weakness and cramps

Reproductive system and breast disorders

Rare: Erectile dysfunction

General disorders and administration site conditions

Common: Fatigue**

Uncommon: Asthenia**

Investigations

Rare: Increased liver enzymes (ALAT, ASAT)

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

4.9 Overdose

Symptoms of bisoprolol overdose*:*

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is

a wide inter-individual variation in sensitivity and in reactions to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

Symptoms of amlodipine overdose*:*

Available data suggest that gross overdose could result in excessive peripheral vasodilatation 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.

Management*:*

In general if overdose occurs, discontinuation of **Emcor FDC** treatment and supportive and symptomatic treatment is recommended including frequent monitoring of cardiac and respiratory function.

Based on the expected pharmacological actions and recommendations for other beta-blockers or calcium-antagonists of the dihydropyridine type, the following general measures may be considered when clinically warranted:

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

Hypotension: Intravenous fluids or 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 temporary pacing.

Acute worsening of heart failure: Administer IV diuretics, positive inotropic medicines, vasodilating medicines.

Bronchospasm: Administer bronchodilatory therapy such as isoprenaline, β_2-sympathomimetic medicines and/or theophylline.

Hypoglycaemia: Administer intravenous glucose

Bisoprolol or amlodipine are hardly dialysable.
Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Category and class: A7.1.3. Other hypotensives

Bisoprolol:

Bisoprolol is a β_1-selective-adrenoreceptor antagonist lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the β_2-receptor of the smooth muscles of bronchi and vessels as well 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 pronounced negative inotropic effect.

Bisoprolol reaches 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. The maximal antihypertensive effect of bisoprolol treatment is generally reached 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. Among others, the depression of plasma rennin activity is discussed as a mechanism of action underlying the antihypertensive effect of beta-blockers.

Amlodipine:

Amlodipine is a dihydropyridine calcium channel blocker. 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:

- 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.
- By means of dilatation 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 case of coronary artery spasm (Prinzmetal’s or variant angina).

BISOPROLOL AND AMLODIPINE COMBINATION

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

Bisoprolol:

The kinetics of bisoprolol are linear and independent of age.

Absorption*:*

Bisoprolol is absorbed almost completely (> 90%) from the gastrointestinal tract. Due to the 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 biotransformation*:*

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. Total clearance is approximately 15 l/h.The elimination half-life in plasma is 10-12 hours.

***Patients with impaired function of the liver or kidneys**:*

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 impairment of the liver or the kidneys.

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.

***Biotransformation 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 7 ml/min/kg (in case of 60 kg-patient: 25 litre/hour). In elderly patients this value is 19 litre/hour.

Use in elderly:

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.

Patients with impaired renal function*:*

Amlodipine is extensively metabolised 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 dialysable.

Patients with impaired hepatic function*:*

The half-life of amlodipine is prolonged in patients with impaired hepatic function. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Interaction studies:

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. Clinical monitoring and dose adjustment may be required. There is no data available regarding the effect of CYP3A4 inducers on amlodipine.

Bisoprolol and amlodipine combination

No pharmacokinetic interaction studies have been performed between the two compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients: Cellulose microcrystalline, magnesium stearate, silica colloidal anhydrous, sodium starch glycolate.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C in the original package in order to protect from light.

6.5 Nature and contents of container

28, 30, 56 or 90 tablets in OPA/Aluminium/Polyvinylchloride/Aluminium blister and carton box.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein

1645

8. REGISTRATION NUMBERS

EMCOR 5/5 FDC:	47/7.1.3/0710
EMCOR 5/10 FDC:	47/7.1.3/0711
EMCOR 10/5 FDC:	47/7.1.3/0712
EMCOR 10/10 FDC:	47/7.1.3/0713

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 September 2022

10. DATE OF REVISION OF THE TEXT

28 March 2025