MERCK

CONCOR® AM

Bisoprolol fumarate/Amlodipine besilate

Antihypertensive

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concor AM 5 mg/5 mg tablets: 5 mg Bisoprolol fumarate, 5 mg Amlodipine (as 6.95 mg Amlodipine besilate) per tablet.

Concor AM 5 mg/10 mg tablets: 5 mg Bisoprolol fumarate, 10 mg Amlodipine (as 13.9 mg Amlodipine besilate) per tablet.

Concor AM 10 mg/5 mg tablet: 10 mg Bisoprolol fumarate and 5 mg Amlodipine (as 6.95 mg Amlodipine besilate) per tablet.

2. PHARMACEUTICAL FORM

Tablet.

Concor AM 5 mg/5 mg tablets: White or almost white, odourless, oblong, slightly convex tablets with a length of 9.5 mm and a width of 4.5 mm 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 AM 5 mg/10 mg tablets: White or almost white, odourless, round, flat, bevel edged tablets of 10 mm 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 AM 10 mg/5 mg tablets: White or almost white, odourless, oval shaped, slightly convex tablets with a length of 13 mm and a width of 7 mm 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.

3. CLINICAL PARTICULARS

3.1 Indications

Concor AM is indicated for the 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.

3.2 Posology and Method of Administration

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

Posology

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.

Patients with hepatic impairment

In case of hepatic impairment elimination of Amlodipine may be elongated. Dosage recommendations concerning Amlodipine have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of Amlodipine have not been studied in severe hepatic impairment. The drug

should therefore be administered with special caution in patients with hepatic impairment (*see section Special Warnings and Precautions for Use*).

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

Patients with renal impairment
No dosage adjustment is required for patients with mild to moderate renal impairment. Changes in Amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable (*see section Special Warnings and Precautions for Use*).

In case of severe renal impairment (creatinin clearance <20 mL/min) the daily dose of Bisoprolol must not exceed 10 mg.

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

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

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

3.3 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 decompensation requiring i.v. inotropic therapy
- 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 and severe forms of Raynaud's syndrome
- Untreated phaeochromocytoma (*see section Special Warnings and Precautions for Use*)
- Metabolic acidosis

In connection with Concor AM
- Hypersensitivity to Amlodipine, Dihydropyridine derivates, Bisoprolol and/or to any of the excipients (*see section List of Excipients*).

3.4 Special Warnings and Special 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, (*see section Pharmacodynamics*). Calcium channel blockers, including Amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function
The half-life of Amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients. Careful monitoring may be required in patients with severe hepatic impairment.

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

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 Posology and Method of Administration*).

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.
- 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 alphareceptor blockade.
- In patients undergoing general anaesthesia beta-blockade 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 beta-blockade be continued perioperatively. The anaesthetist 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 nonselective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airway diseases, unless there are compelling clinical reasons for their use. Where such reasons exists, Concor AM 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 beta2-stimulants may have to be increased.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction
In connection with Amlodipine
Effects of other medicinal products on Amlodipine
- CYP3A4 inhibitors: Concomitant use of Amlodipine with strong or moderate inhibitors of CYP3A4 (e.g. protease inhibitors like Indinavir, Saquinavir and Ritonavir, azole antifungals such as

Fluconazole and Itraconazole, macrolides like Erythromycin or Clarithromycin, Verapamil or Diltiazem) may give rise to significant increase in Amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
- CYP3A4 inducers: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of Amlodipine may vary. 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 bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

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.

Effects of Amlodipine on other medicinal products
The blood pressure lowering effects of Amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, Amlodipine did not affect the pharmacokinetics of Atorvastatin, Digoxin or Warfarin.

Simvastatin
Co-administration of multiple doses of 10 mg of Amlodipine with 80 mg Simvastatin resulted in a 77% increase in exposure to Simvastatin compared to Simvastatin alone. Limit the dose of Simvastatin in patients on Amlodipine to 20 mg daily.

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.

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.

Laboratory parameters
There is no effect of Amlodipine on laboratory parameters.

In connection with Bisoprolol
Combinations not recommended
- *Calcium antagonists of Verapamil type* and to a lesser extent of Diltiazem type: Negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of Verapamil in patients on beta-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

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 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. Blockade 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 Special Warnings and Precautions for Use*).
- *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 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.

3.6 Pregnancy, Lactation, and Fertility
Pregnancy
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. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

The safety of Amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (*see section Preclinical Safety Data*).

Concor AM is not recommended during pregnancy unless clearly necessary. If treatment with Concor AM 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.

Lactation
There is no information on whether Bisoprolol is excreted in breast 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 AM is not recommended during breast-feeding.

A decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

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. Clinical data are insufficient regarding the potential effect of Amlodipine on fertility. In one rat study, adverse effects were found on male fertility (*see section Preclinical Safety Data*). Bisoprolol had no influence on fertility or on general reproduction performance in animal studies (*see section Preclinical Safety Data*).

3.7 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.

3.8 Undesirable Effects

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

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 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

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Insomnia, mood changes (including anxiety), depression
Rare: Confusion

Nervous system disorders
Common: Headache, dizziness, somnolence (especially at the beginning of the treatment)
Uncommon: Syncope, hypoaesthesia, paraesthesia, dysgeusia, tremor
Very rare: Hypertonia, peripheral neuropathy

Eye disorders
Common: Visual disturbances (including diplopia)

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Common: Palpitation
Uncommon: Arrhythmia (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: Dyspnoe
Uncommon: Cough, rhinitis

Gastrointestinal disorders
Common: nausea, abdominal pain, dyspepsia, altered bowel habits (including diarrhoea and constipation)
Uncommon: Vomiting, dry mouth
Very rare: Gastritis, gingival hyperplasia, pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis*, jaundice*, hepatic enzyme increased*

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema, urticaria
Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Frequency 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 disorder
Rare: Nightmare, hallucination

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 preexisting 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

3.9 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 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.

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

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 blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of Amlodipine 10 mg 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 beta-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
In general, 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 pharmacological 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 cardiac pacemaker insertion.

Acute worsening of heart failure: iv. diuretics, positive inotropic agents, vasodilating agents should be administered.

Bronchospasm: Bronchodilator therapy such as Isoprenaline, beta2-sympathomimetic drugs and/or Aminophylline should be administered.

Hypoglycaemia: iv. glucose should be administered.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic Properties

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

ATC code: C07FB07.

Mechanism of action of Amlodipine
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of Amlodipine is due to a direct relaxant effect on vascular smooth muscle.

The precise mechanism by which Amlodipine relieves angina has not been fully determined, but Amlodipine reduces total ischaemic burden by the following two actions:
- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart remains stable, this unloading of the heart reduces, myocardial energy consumption and oxygen requirements.
- The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic effects
In patients with hypertension, once daily dosing 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 Amlodipine administration.

In patients with angina, once daily administration of Amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablets consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids, and is suitable for use in patients with asthma, diabetes, and gout.

Mechanism of action of Bisoprolol
Bisoprolol is a potent, highly beta1-selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilising activity.

It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, Bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range. 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).

4.2 Pharmacokinetic Properties
Amlodipine
Absorption, distribution, plasma protein binding
After oral administration of therapeutic doses, Amlodipine is well absorbed with peak blood levels

between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%.

The volume of distribution is approximately 21 L/kg. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing. In vitro studies have shown that approximately 97.5% of circulating Amlodipine is bound to plasma proteins.

The bioavailability of Amlodipine is not affected by food intake.

Biotransformation/elimination
The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elderly population
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 studied.

Renal impairment
The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Hepatic impairment
Very limited clinical data are available regarding Amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of Amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Bisoprolol
Absorption
Bisoprolol is absorbed almost completely (> 90%) 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. 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 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 L/h.

The elimination half-life in plasma is 10-12 hours.

The kinetics of bisoprolol are linear and independent of age.

Combination product
A pharmacokinetic interaction study demonstrated no interaction between the two compounds.

4.3 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 10 mg 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 10 mg/kg/day Amlodipine (8 times the maximum recommended human dose of 10 mg/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 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 test 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.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients
Colloidal anhydrous silica
Magnesium stearate
Sodium starch glycolate (type A)
Microcrystalline cellulose

5.2 Shelf-life
The expiry date is indicated on the packaging.

5.3 Special Precautions for Storage
Do not store above 30ºC.

5.4 Package Quantities and Registration Number

Concor AM 5 mg/5 mg tablets	Box of 3 blisters @ 10 tablets	Reg. No. DKI1952900110A1
Concor AM 5 mg/10 mg tablets	Box of 3 blisters @ 10 tablets	Reg. No. DKI1952900110C1
Concor AM 10 mg/5 mg tablets	Box of 3 blisters @ 10 tablets	Reg. No. DKI1952900110B1

6. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Concor AM 5mg/5 mg	02 Jul 2019/xxxxxx
Concor AM 5 mg/10 mg	02 Jul 2019/xxxxxx
Concor AM 10 mg/5 mg	02 Jul 2019/xxxxxx

7. DATE OF REVISION OF THE TEXT
SmPC based on CCDS version 9.0 (02-Jun-2022)

BPOM approval of the latest update xxxxxx

8. CLASSIFICATION OF MEDICINE
Medicinal product subject to medical prescription. Obat Keras.

HARUS DENGAN RESEP DOKTER
On medical prescription only

Manufactured by
EGIS Pharmaceuticals Plc.,
Budapest, Hungary

For
Merck Healthcare KGaA,
Darmstadt, Germany

Imported by
PT Merck Tbk,
Jakarta, Indonesia

INFORMASI UNTUK PASIEN

Concor® AM

Bisoprolol fumarate/Amlodipine besilate

Antihipertensi

Baca petunjuk ini dengan cermat sebelum mulai minum obat ini karena mengandung informasi penting untuk Anda.

- Simpan lembar petunjuk ini, Anda mungkin akan memerlukannya kembali.
- Jika Anda mempunyai pertanyaan lebih lanjut, harap menghubungi dokter atau apoteker.
- Obat ini diresepkan hanya untuk Anda, jangan diberikan kepada orang lain karena dapat membahayakan orang tersebut meskipun terdapat gejala yang sama pada orang tersebut.
- Jika Anda mengalami efek samping, harap hubungi dokter atau apoteker. Termasuk efek samping yang tidak terdapat pada petunjuk ini *(lihat bagian 4 Efek samping yang mungkin terjadi)*.

Petunjuk ini terdiri dari informasi sebagai berikut:

1 Apa yang dimaksud dengan Concor AM dan apa kegunaannya

Concor AM diindikasikan untuk pengobatan tekanan darah tinggi sebagai terapi pengganti pada pasien yang cukup terkontrol dengan produk-produk tunggal yang diberikan bersamaan pada tingkat dosis yang sama sebagai kombinasi, tetapi sebagai tablet terpisah.

2 Apa yang perlu Anda ketahui sebelum Anda minum Concor AM

Jangan minum Concor AM jika:

- Anda alergi terhadap amlodipine, bisoprolol, turunan dihydropyridine maupun salah satu dari bahan-bahan yang terdapat dalam formula obat ini (lihat bagian 6 Isi dari kemasan dan informasi lain).
- Dalam keadaan tekanan darah sangat rendah sekali.
- Dalam keadaan asma berat.
- Masalah berat pada sirkulasi darah di tungkai Anda (seperti sindroma Raynaud), yang mungkin menyebabkan jari tangan dan jari kaki seperti tergelitik atau berubah pucat atau biru.
- Dalam keadaan menderita feokromositoma tak terobati, yaitu tumor langka pada sumsum kelenjar adrenal.
- Dalam kondisi asidosis metabolik, yaitu suatu kondisi ketika terdapat terlalu banyak asam dalam darah.

Jangan minum obat ini jika Anda memiliki salah satu masalah jantung berikut:

- Anda memiliki penyempitan serius pada saluran keluar ventrikel kiri (contohnya stenosis aorta tingkat tinggi).
- Anda menderita gagal jantung akut.
- Syok kardiogenik, yang merupakan kondisi jantung akut yang serius yang menyebabkan tekanan darah rendah dan kegagalan sirkulasi darah.

DISETUJUI OLEH BPOM : 14/03/2024

ID : EREG10014912400038
EREG10014912400039
EREG10014912400040

- Memburuknya gagal jantung yang membutuhkan suntikan obat ke pembuluh darah, yang meningkatkan kekuatan kontraksi jantung.
- Dalam keadaan denyut jantung lambat.

Jika Anda berpikir Anda menderita salah satu penyakit di atas, tanyakan pada dokter apakah Anda dapat minum obat ini.

Peringatan dan Pencegahan
Jika Anda memiliki salah satu dari kondisi berikut beritahu dokter Anda sebelum meminum obat ini, Dokter mungkin akan memberikan perawatan khusus (misalnya memberikan perlakuan tambahan atau melakukan pemeriksaan lebih sering):
- Usia lanjut
- Gagal jantung
- Diabetes disertai kadar gula darah yang sangat bervariasi
- Puasa yang ketat
- Penyakit jantung tertentu seperti gangguan irama jantung, atau nyeri dada yang parah saat istirahat (angina Prinzmetal)
- Masalah penurunan sirkulasi darah pada kaki dan tangan
- Psoriasis (Ruam kulit bersisik)
- Hipertireosis (Gangguan tiroid)
- Gangguan hati atau ginjal
- Dalam keadaan menderita feokromositoma tak terobati, yaitu tumor langka pada sumsum kelenjar adrenal

Selain itu, harap memberitahu dokter Anda jika akan mendapat:
- Terapi desensitisasi (misalnya untuk pencegahan alergi serbuk bunga (hay fever)), karena obat mungkin akan membuat Anda mengalami reaksi alergi, atau reaksi tersebut mungkin menjadi lebih parah.
- Anestesi (misalnya untuk operasi), karena obat dapat mempengaruhi bagaimana tubuh Anda bereaksi terhadap kondisi sedasi.

Jika Anda memiliki penyakit paru-paru kronis atau asma agak parah segera informasikan ke dokter Anda terutama ketika Anda mulai mengalami kesulitan dalam bernapas, batuk, sesak setelah berolahraga, dan sebagainya Ketika menggunakan obat ini.

Anak-anak dan Remaja
Concor AM tidak dianjurkan untuk digunakan pada anak-anak di bawah usia 18 tahun dikarenakan kurangnya data khasiat dan keamanan

Obat Lain dan Concor AM
Pengobatan dan efek samping obat ini dapat menjadi bias oleh obat lain yang diminum secara bersamaan.

Interaksi dapat timbul, bahkan jika obat lainnya telah diminum hanya dalam waktu singkat.

Beritahu dokter atau apoteker jika Anda sedang minum, baru saja minum, atau mungkin akan minum obat lainnya.

<u>Pemberian obat berikut bersamaan dengan Concor AM tidak dianjurkan:</u>
- Verapamil dan diltiazem tipe pemblok kanal kalsium: Obat-obatan tertentu yang digunakan untuk pengobatan tekanan darah tinggi, dan angina pektoris atau detak jantung tidak teratur.
- Obat-obatan tertentu yang digunakan untuk mengobati tekanan darah tinggi seperti clonidine, methyldopa, moxonodine, rilmenidine. Namun, jangan berhenti minum obat sebelum berkonsultasi terlebih dahulu dengan dokter Anda.

Obat-obatan berikut dapat diberikan bersamaan dengan Concor AM dalam kondisi tertentu dengan perhatian khusus di bawah pengawasan medis:

- Beberapa obat pengatur denyut jantung (disopyramide, quinidine, lidocaine, phenytoin, flecainide, propafenone, amiodarone). Obat-obatan tertentu yang digunakan untuk mengobati denyut jantung yang tidak teratur atau tidak normal.
- Obat beta bloker secara lokal (misalnya tetes mata timolol untuk mengobati glaukoma).
- Parasimpatomimetik. Obat-obat tertentu yang digunakan untuk mempotensiasi fungsi otot polos pada penyakit lambung, usus halus, kandung kemih, dan glaucoma.
- Insulin dan antidiabetes oral.
- Hipnotik, obat anestesi.
- Glikosida jantung (digitalis), obat tertentu yang digunakan untuk mengobati gagal jantung.
- Obat antiinflamasi non-steroid (OAINS). Obat ini dapat diberikan untuk mengobati radang sendi, nyeri atau peradangan (misalnya ibuprofen atau diclofenac).
- Simpatomimetik (misal isoprenaline, dobutamine, norepinephrine, epinephrine). Obat-obatan tertentu yang digunakan untuk pengobatan pada masalah jantung akut.
- Setiap obat yang dapat menurunkan tekanan darah yang baik itu berupa efek yang diinginkan atau efek yang tidak diinginkan seperti antihipertensi, obat-obatan tertentu untuk depresi (antidepresan trisiklik seperti imipramine atau amitriptyline), obat-obatan tertentu yang digunakan untuk mengobati epilepsi atau selama anestesi (barbiturate seperti fenobarbital), atau obat-obatan tertentu untuk mengobati gangguan mental yang ditandai dengan hilangnya kontak dengan kenyataan (phenothiazin seperti levomepromazine)
- Tacrolimus, obat yang digunakan untuk mengubah cara kerja sistem kekebalan tubuh.
- Cyclosporine, obat-obat tertentu yang digunakan untuk pengobatan gangguan kekebalan tubuh.
- Dantrolene, infus untuk kelainan suhu tubuh yang parah.
- Simvastatin, obat penurun kolesterol.

Dokter perlu mempertimbangkan efek yang mungkin terjadi untuk pemberian obat berikut bersamaan dengan Concor AM:

- Mefloquine, obat untuk mencegah atau mengobati malaria.
- Inhibitor monoamino-oksidase/MAO (kecuali inhibitor MAO-B), untuk pengobatan depresi.
- Obat-obatan yang mempengaruhi metabolism amlodipine atau bisoprolol, misalnya:
  - Fluconazole dan itraconazole (obat antijamur)
  - Indinavir, saquinavir, dan ritonavir (disebut inhibitor protease digunakan untuk mengobati HIV)
  - Rifampicin, erythromycin, clarithromycin (antibiotik)
  - Hypericum perforatum (St. John's Wort)

Concor AM dengan Makanan, Minuman, dan Alkohol
Alkohol dapat meningkatkan efek penurunan tekanan darah.

Jus grapefruit dan grapefruit sebaiknya tidak dikonsumsi oleh pasien yang sedang minum Concor AM. Hal ini karena grapefruit dan jus grapefruit dapat menyebabkan naiknya kadar zat aktif amlodipine dalam darah, dapat menyebabkan peningkatan efek penurunan tekanan darah Concor AM yang tak terprediksi.

Kehamilan dan Menyusui
Kehamilan
Sebagaimana tidak terdapat jumlah studi klinis yang tepat pada wanita hamil, obat dapat diberikan hanya setelah dokter mempertimbangan secara hati-hati rasio risiko/keuntungannya, sehingga jangan lupa memberitahukan dokter jika Anda hamil atau merencanakan kehamilan. Pada kasus pemberian saat kehamilan, pemantauan secara cermat kondisi janin dan bayi baru lahir mungkin diperlukan.

Menyusui

Amlodipine masuk ke dalam air susu ibu dalam jumlah kecil. Concor AM tidak dianjurkan untuk ibu menyusui.

Mengemudi dan Menjalankan Mesin
Concor AM dapat mempengaruhi kemampuan untuk mengemudi atau menjalankan mesin karena menyebabkan pusing, sakit kepala, kelelahan atau mual; terutama ketika Anda memulai pengobatan atau jika pengobatan Anda berubah dan ketika Anda minum alkohol; oleh karena itu dokter akan memutuskan secara perorangan pada dosis berapa Anda dapat mengemudi atau menjalankan mesin.

Informasi Terkait Bahan Concor AM
Tiap tablet obat ini mengandung kurang dari 1 mmol sodium (23 mg), sehingga diartikan ‘bebas sodium’.

3 Bagaimana meminum Concor AM

Selalu minum obat ini persis seperti yang dokter beritahukan kepada Anda. Tanyakan kembali kepada dokter atau apoteker jika Anda tidak yakin.

Pengobatan dengan obat ini membutuhkan pemantauan berkala oleh dokter Anda. Hal ini terutama diperlukan diawal pengobatan, selama peningkatan dosis, dan ketika Anda menghentikan pengobatan.

Dosis yang dianjurkan adalah satu tablet dosis yang diresepkan kepada Anda.

Biasanya tidak diperlukan penyesuaian dosis pada penyakit hati atau ginjal ringan hingga sedang. Pada penyakit hati atau ginjal yang serius dosis dapat dimodifikasi.

Pemberian
Concor AM harus diminum pada pagi hari, dengan atau tanpa makanan, dengan sedikit cairan tanpa mengunyah tablet.

Garis bagi pada tablet hanya untuk membantu Anda membagi tablet jika Anda kesulitan menelan obat dalam sekali telan.

Jika Anda merasakan efek terapi Concor AM terlalu kuat atau terlalu lemah, konsultasikan ke dokter atau apoteker.

Lanjut Usia
Tidak diperlukan penyesuaian dosis pada pasien lanjut usia, namun, disarankan hati-hati ketika dosis ditingkatkan.

Jika Anda Minum Concor AM Lebih dari Seharusnya
Jika Anda minum Concor AM lebih dari seharusnya, segera konsultasikan ke dokter.

Kelebihan cairan dapat menumpuk di paru-paru Anda (edema paru) menyebabkan sesak napas yang mungkin timbul hingga 24-48 jam setelah asupan.

Jika Anda Lupa Minum Concor AM
Minum dosis yang terlewat sesegera mungkin. Jika sudah akan waktunya minum dosis berikutnya, jangan minum dosis ganda untuk mengganti dosis yang terlewatkan, karena Anda tidak dapat mengganti jumlah obat yang terlewat melainkan hanya akan meningkatkan risiko overdosis.

Jika Anda Berhenti Minum Concor AM
Jangan berhenti minum obat secara mendadak, atau mengubah dosis yang dianjurkan sebelum konsultasi ke dokter, karena dalam beberapa kasus gagal jantung dapat memburuk sementara waktu. Pengobatan

tidak dapat dihentikan secara mendadak terutama pada pasien dengan penyakit koroner. Jika diperlukan penghentian obat, dosis harus dikurangi secara bertahap.

Jika Anda memiliki pertanyaan lebih lanjut mengenai cara minum obat ini, tanyakan dokter atau apoteker.

4 Efek samping yang mungkin terjadi

Seperti halnya semua obat, obat ini dapat menyebabkan efek samping, meski tidak terjadi pada setiap pasien.

Untuk mencegah terjadinya reaksi yang bersifat serius, bicarakan dengan dokter Anda segera jika timbul efek samping yang parah, terjadi tiba-tiba atau memburuk dengan cepat.

Jika Anda merasa pusing atau lemah, atau memiliki kesulitan bernapas, hubungi dokter sesegera mungkin.

Efek samping lebih lanjut tercantum di bawah ini sesuai dengan kejadian yang sering terjadi:

Sangat Umum (dapat terjadi pada lebih dari 1 dalam 10 pasien)
Berhubungan dengan amlodipine
Edema (pembengkakan pada tubuh).

Umum (dapat terjadi pada 1 dari 10 pasien)
Berhubungan dengan amlodipine
Sakit kepala, pusing, mengantuk (terutama pada awal pengobatan), gangguan penglihatan (termasuk pandangan ganda), palpitasi (detak jantung lebih cepat), flush (sensasi hangat dan kemerahan di wajah), sesak, mual, sakit perut, gangguan pencernaan, perubahan kebiasaan buang air besar (termasuk diare dan sembelit), pembengkakan pergelangan kaki, kram otot, letih, kelelahan (asthenia).

Berhubungan dengan bisoprolol
Pusing**, sakit kepala**, merasa kedinginan dan mati rasa pada tangan dan kaki, keluhan pada saluran pencernaan (misal mual, muntah, diare, dan sembelit), letih**.

Tidak Umum (dapat terjadi pada 1 dari 100 pasien)
Berhubungan dengan amlodipine
Insomnia, perubahan suasana hati (termasuk cemas), depresi, pingsan, kepekaan fungsi rasa berkurang, sensasi rasa tanpa sebab yang jelas, mulut asam, tremor, telinga berdenging, aritmia, tekanan darah rendah, batuk, rinitis, muntah, mulut kering, rambut rontok, peradangan pembuluh darah pada kulit, perubahan warna kulit, keringat berlebih, sensasi gatal dan tidak nyaman pada kulit, kulit kemerahan, ruam pada kulit, biduran, nyeri sendi, nyeri otot, nyeri punggung, gangguan berkemih, gangguan berkemih pada malam hari, frekuensi kencing naik, impotensi, pembesaran jaringan kelenjar payudara pada pria, nyeri dada, nyeri, badan lemas, berat badan naik, berat badan turun.

Berhubungan dengan bisoprolol
Depresi, gangguan tidur, gangguan irama jantung, pemburukan gagal jantung yang sudah ada sebelumnya, denyut jantung lambat, tekanan darah turun, masalah pernapasan pada pasien dengan asma atau dengan riwayat penyakit paru obstruktif, pelemahan otot, kram, kelelahan**.

Jarang (dapat terjadi pada 1 dari 1000 pasien)
Berhubungan dengan amlodipine
Kebingungan.

Berhubungan dengan bisoprolol
Kadar lemak naik, mimpi buruk, halusinasi, pingsan, produksi air mata berkurang (hal ini harus

dipertimbangkan apabila pasien menggunakan lensa kontak), pendengaran menurun, pilek alergi, hepatitis, reaksi hipersensitivitas (misal gatal, *flush*/sensasi hangat pada wajah, ruam), impotensi, enzim hati meningkat.

Sangat Jarang (dapat terjadi pada 1 dari 10.000 pasien)
Berhubungan dengan amlodipine
Jumlah sel darah putih dan sel darah merah turun, reaksi alergi, kadar gula darah naik, kemampuan kontraksi otot berkurang, kerusakan saraf tepi, serangan jantung, peradangan pembuluh darah, peradangan dinding lambung, peradangan pada gusi, radang pada kelenjar pankreas, hepatitis*, penyakit kuning*, enzim pankreas meningkat*, pembengkakan kulit, reaksi alergi pada kulit, kulit kemerahan dan mengelupas, sindrom Stevens- Johnson (reaksi alergi kompleks), sensitive terhadap cahaya.

Berhubungan dengan bisoprolol
Mata iritasi dan kemerahan, rambut rontok di mana beta bloker menimbulkan atau memperburuk psoriasis (ruam kulit bersisik) atau menyebabkan kerusakan kulit menyerupai psoriasis.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
Berhubungan dengan amlodipine
Nekrolisis epidermis toksik yaitu kelainan kulit yang sangat serius ditandai dengan kerusakan jaringan kulit yang cukup luas.

*bersamaan dengan kolestasis (aliran empedu terhambat) dalam kebanyakan kasus.
**gejala-gejala ini muncul terutama pada awal pengobatan. Gejala-gejala tersebut umumnya ringan dan sering kali akan hilang dalam waktu 1-2 minggu.

Pelaporan Efek Samping
Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker Anda. Juga termasuk kemungkinan efek samping yang tidak tercantum dalam petunjuk ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5 Bagaimana menyimpan Concor AM

Simpan obat Concor AM jauh dari jangkauan anak-anak.

Jangan simpan obat di atas suhu 30°C.

Jangan minum obat setelah tanggal kedaluwarsa yang tertera pada kemasan berakhir.

Jangan minum obat apabila Anda menyadari tablet rusak berubah warnanya.

Jangan membuang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana membuang obat-obatan yang tidak diperlukan. Hal ini untuk menjaga lingkungan.

6 Isi dari kemasan dan informasi lain

Isi dari Kemasan
Zat aktif obat:
Concor AM 5 mg/5 mg: 5 mg Bisoprolol fumarate dan 5 mg Amlodipine (dalam bentuk besilate).
Concor AM 5 mg/10 mg: 5 mg Bisoprolol fumarate dan 10 mg Amlodipine (dalam bentuk besilate).
Concor AM 10 mg/5 mg: 10 mg Bisoprolol fumarate dan 5 mg Amlodipine (dalam bentuk besilate).

Komposisi lain:
Microcrystalline cellulose, Sodium starch glycolate (type A), Magnesium stearate, Colloidal anhydrous

silica.

Bentuk Tablet
Concor AM 5 mg/5 mg: Tablet putih atau hampir putih, tidak berbau, lonjong, sedikit cembung dengan panjang 9,5 mm dan lebar 4,5 mm dengan garis bagi di satu sisi dan tercetak MS timbul di sisi lainnya. Garis bagi pada tablet hanya untuk membantu membagi tablet guna mempermudah menelan obat, bukan untuk membagi dosis sama rata.

Concor AM 5 mg/10 mg: Tablet putih atau hampir putih, tidak berbau, bulat, pipih, bertepi miring dengan diameter 10 mm dengan garis bagi di satu sisi dan tercetak MS timbul di sisi lainnya. Garis bagi pada tablet hanya untuk membantu membagi tablet guna mempermudah menelan obat, bukan untuk membagi dosis sama rata.

Concor AM 10 mg/5 mg: Tablet putih atau hampir putih, tidak berbau, oval, sedikit cembung dengan panjang 13 mm dan lebar 7 mm dengan garis bagi di satu sisi dan tercetak MS timbul di sisi lainnya. Garis bagi pada tablet hanya untuk membantu membagi tablet guna mempermudah menelan obat, bukan untuk membagi dosis sama rata.

Kemasan dan Nomor Izin Edar

Concor AM 5 mg/5 mg	Dus, 3 blister @ 10 tablet	Reg. No. DKI1952900110A1
Concor AM 5 mg/10 mg	Dus, 3 blister @ 10 tablet	Reg. No. DKI1952900110C1
Concor AM 10 mg/5 mg	Dus, 3 blister @ 10 tablet	Reg. No. DKI1952900110B1

Tanggal Perubahan Informasi
Informasi Untuk Pasien ini selaras dengan SmPC based on CCDS version 9.0 (02-Jun-2022)
Persetujuan BPOM terhadap pembaruan terakhir xxxxxx

HARUS DENGAN RESEP DOKTER

Diproduksi oleh
EGIS Pharmaceuticals Plc.,
Budapest, Hungaria

Untuk
Merck Healthcare KGaA,
Darmstadt, Jerman

Diimpor oleh
PT Merck Tbk,
Jakarta, Indonesia