For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CORBIS AM 2.5/2.5 CORBIS AM 2.5/5

1. Generic Name

Amlodipine and Bisoprolol Fumarate Tablets (2.5mg + 2.5mg & 2.5mg + 5mg)

2. Qualitative and quantitative Composition:

Each film coated tablets contains:

Amlodipine Besylate I.P.

Equivalent to Amlodipine …… 2.5mg/2.5mg

Bisoprolol Fumarate I.P…… 2.5mg/5mg

Excipients…… q.s.

Colours: Ferric Oxide USP NF Red, Ferric Oxide USP NF Yellow & Titanium Dioxide I.P

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Polyethylene Glycol, Titanium Dioxide, Red Iron Oxide, Yellow Iron Oxide, Isopropyl Alcohol.

3. Dosage form and strength

Dosage form: Film coated tablets

Strength: Amlodipine and Bisoprolol Fumarate (2.5mg + 2.5mg & 2.5mg + 5mg)

4. Clinical particulars

4.1. Therapeutic indication

For the treatment of mild to moderate hypertension.

4.2. Posology and method of administration

Posology

Corbis AM 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.

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.

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.

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.

Paediatric population

The safety and efficacy of Amlodipine and Bisoprolol Fumarate in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

Amlodipine and Bisoprolol Fumarate tablet 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 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.
- Metabolic acidosis

In connection with Corbis AM

- Hypersensitivity to amlodipine, dihydropyridine derivates, bisoprolol and/or to any of the excipients

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.

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

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.

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.
- 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 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 bradyarrhythmia's, 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 (betal) 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 airway diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, Amlodipine and Bisoprolol Fumarate 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 2-stimulants may have to be increased.

4.5. Drugs interactions

<u>In connection with Amlodipine:</u>

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: There is no data available regarding the effect ofCYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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.

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

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.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, or warfarin.

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 -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.

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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, -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 -adrenoceptor blockers is necessary, I-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.

Amlodipine and Bisoprolol Fumarate is not recommended during pregnancy unless clearly necessary. If treatment with Amlodipine and Bisoprolol Fumarate 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 or amlodipine is excreted in human milk. Therefore, administration of Amlodipine and Bisoprolol Fumarate 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. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

Bisoprolol had no influence on fertility or on general reproduction performance in animal studies.

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 given according to the following frequency grouping:

Very common (2 1/10) Common (2 1/100 to< 1/10) Uncommon (2 1/1,000 to< 1/100) Rare (2 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.

General disorders and administration site conditions	
Very common	Oedema
Common	Fatigue, asthenia
Uncommon	Chest pain, pain, malaise
Nervous system disorders	
Common	Somnolence, dizziness, headache
Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Psychiatric disorders	
Uncommon	Depression, mood changes (including anxiety), insomnia
Rare	Confusion
Eye disorders	
Commons	Visual disturbances (including diplopia)

Ear and labyrinth disorderd	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitation
Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia, 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 (in most cases with cholestasis)
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
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	Impotence, gynecomastia
Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	

Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Exceptional cases	
Exceptional	Extrapyramidal syndrome

In connection with Bisoprolol

General disorders and administration site conditions	
Common	Fatigue, asthenia
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 (consider 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 cause psoriasis-like skin disorder
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle weakness and cramps
Reproductive system and breast disorders	
Rare	Impotence

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

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 vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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 -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 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: I.V. diuretics, positive inotropic agents, vasodilating agents should be administered.

Bronchospasm: Bronchodilator therapy such as isoprenaline, 2-sympathomimetic drugs and/or aminophylline should be administered.

Hypoglycaemia: I.V. glucose should be administered.

5. Pharmacological properties

5.1. Mechanism of Action

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:

a) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

b) 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).

Bisoprolol

Bisoprolol is a potent, highly 1-selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilising activity.

It only shows low affinity to the 2-receptor of the smooth muscles of bronchi and vessels as well as to the 2-receptors concerned with metabolic regulation. Therefore, bisoprolol is

generally not to be expected to influence the airway resistance and 2-mediated metabolic effects. Its 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.

5.2. Pharmacodynamic properties

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 tablet 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.

Pharmacodynamic effects of the combination product

This combination allows to increase the antihypertensive and anti-angina! 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).

5.3. 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 I/kg. 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.

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%.

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.

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 I/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 1/h.

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 exist, - according to the results of bioequivalence study - the extent of this hypothetic interaction must be the same in case of taking Amlodipine and Bisoprolol Fumarate, than in case of taking the two compounds separately at the same dose levels as in the combination.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

In connection with Amlodipine:

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility ofrats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a 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.

Carcinogenesis, mutagenesis:

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of0.5, 1.25, and 2.5 mg/kg/day, showed no evidence ofa carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

In connection with Bisoprolol:

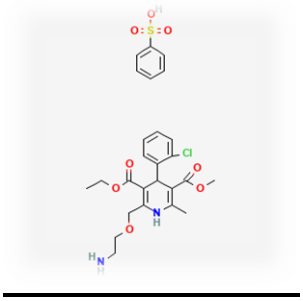
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. During reproduction toxicology tests bisoprolol had no influence on fertility or general reproduction ability.

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.

7. Description

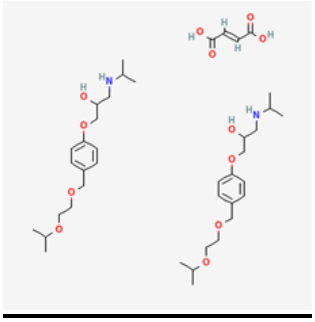
Amlodipine Besylate

Amlodipine Besylate is benzenesulfonic acid;3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
The empiric formula of $C_{26}H_{31}ClN_2O_8S$ and its molecular weight is 567.1 g/mol. Its structural formula is:



Bisoprolol Fumarate

Bisoprolol Fumarate is (E)-but-2-enedioic acid;1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl)phenoxy]propan-2-ol. The empiric formula of $C_{40}H_{66}N_2O_{12}$ and its molecular weight is 767.0 g/mol. Its structural formula is:



CORBIS AM 2.5/2.5 is Orange coloured, round, biconvex, film coated tablets, plain on both sides.

CORBIS AM 2.5/5 is Orange coloured, Capsule shape, biconvex, film coated tablets, plain on both sides.

The excipients used are Dibasic Calcium Phosphate, Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Polyethylene Glycol, Titanium Dioxide, Red Iron Oxide, Yellow Iron Oxide, Isopropyl Alcohol.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

CORBIS AM is packed in 10 Tablets.

8.4. Storage and handing instructions

Store below 30°C.

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Exemed Pharmaceuticals.
Plot No. 133/1 & 133/2, GIDC,
Selvas Road, Vapi-396195,
Dist. Valsad, Gujarat, India

11. Details of permission or licence number with date

Mfg Lic No. G/25/2011 issued on 30.05.2025.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ CORBIS AM 2.5/2.5mg, 2.5/5 mg/SEP-25/01/PI