For the use only of Registered Medical Practitioner

1. Generic Name & Brand Name

Bisoprolol and Amlodipine Tablets
Bisosafe™ AM 2.5

Bisoprolol and Amlodipine Tablets
Bisosafe™ AM 5

2. Qualitative and Quantitative Composition:

Bisosafe™ AM 2.5
Each film coated tablets contains:
Bisoprolol Fumarate I.P.…2.5 mg
Amlodipine Besilate I.P.
Equivalent to Amlodipine…5 mg
Excipients……q.s.
Colours: Quinoline Yellow Lake & Titanium Dioxide I.P.

Bisosafe™ AM 5
Each film coated tablets contains:
Bisoprolol Fumarate I.P.…5 mg
Amlodipine Besilate I.P.
Equivalent to Amlodipine…5 mg
Excipients……q.s.
Colours: Ponceau 4R lake & Titanium Dioxide I.P.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of mild to moderate hypertension in adults.

4.2 Posology and method of administration

Posology
This combination used in patients whose blood pressure is adequately controlled with separately administered mono component preparations 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. In case of severe hepatic impainnent the daily dose of bisoprolol must not exceed 10mg.

Patients with renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable. In case of severe renal impairment (creatinine 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 Bisoprolol Fumarate & Amlodipine in children and adolescents below the age of 18 years have not been established.

No data are available.

Method of administration Bisoprolol Fumarate & Amlodipine 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)
- Hemodynamically 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 Bisoprolol Fumarate & Amlodipine Combination:

Hypersensitivity to amlodipine, dihydropyridine derivates,
Bisoprolol and/or to any of the excipients used in product.

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 Ill 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 ischemic 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 hypoglycemia (e.g. tachycardia, palpitations, sweating) can be masked.

➔ Strict fasting/diet.

➔ Concomitant desensitization 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.

➔ Printz metal'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 betablockers (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 anesthetist must be aware of betablockade 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 (β -1) 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 exist, Bisoprolol Fumarate & Amlodipine combination may be used with caution. In bronchial asthma, 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 β 2-stimulants may have to be increased.

4.5 Drug Interactions

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, diltiazem) may give rise to significant increase in Amlodipine exposure resulting in 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 of CYP3A4 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. In clinical interaction studies grapefruit juice, cimetidine, aluminum/ magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products:

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

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

Simvastatin: Combination with amlodipine may lead to an increase in simvastatin plasma level.

Simvastatin doses of more than 20 mg daily are not recommended in patients treated with amlodipine. 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, atrioventricular conduction, and blood pressure. Intravenous administration of verapamil in patients on P-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 maybe potentiated.
Class Ill antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time maybe potentiated.
Parasympathomimetic drugs: Concomitant use may increase atria-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 hypoglycemia.
Anaesttietic 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 β and α 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 more likely with nonselective beta blockers.
Concomitant use with anti-hypertensive 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.
Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug metabolizing enzymes.
Normally no dosage adjustment is necessary.
Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy: Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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, Beta 1-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.
Bisoprolol Fumarate & Amlodipine is not recommended during pregnancy unless clearly necessary. If treatment with Bisoprolol Fumarate & Amlodipine is considered necessary, the uteroplacental blood low and the fetal growth should be closely monitored. In case of harmful effects on pregnancy or the fetus 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 Bisoprolol Fumarate & Amlodipine 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 patient's 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 (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 reported adverse reactions during treatment are somnolence, dizziness,
headache, palpitations, flushing, abdominal pain, nausea, ankle
swelling, and fatigue
Blood and lymphatic system disorders
Very rare Leukopenia, thrombocytopenia.
Immune system disorders
Very rare Allergic reactions
Metabolism and nutrition disorders
Very rare: Hyperglycemia
Psychiatric disorders
Uncommon: Depression, mood changes {including anxiety}, insomnia
Rare: Confusion
Nervous system disorders
Common: Somnolence, dizziness, headache (especially at the beg inning of the treatment)
Uncommon:
Very rare: Hypertonia, penpheral neuropathy
Eye disorders
Common: Visual disturbances (including diplopia)
Ear and labyrinth disoroers
Uncommon: Tinnitus
Cardiac disorders
Common: Palpitation
Uncommon: Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrilation)
Very rare: Myocardial infarction
Vascular disorders
Palpitation
Arrhythmia (including bradycardia ventricular tachycardia and atnal fibrilation)
Myocardial infarction
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis
Respiratory, thoracic, mediastinal disorders
Common: Dyspnea
Uncommon: Cough, rhinitis
Gastrointestinal disorders
Common: Abdominal pain, nausea, dyspepsia, altered
bowel habits (including diarrhea 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 discoloration,
Very rare:
Hyperhidrosis, pruritus, rash, exanthema, urticaria
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
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 impairment, 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, 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, diarrhea, 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: Impotence General disorders and
administration site conditions
Common: Fatigue
Uncommon: Asthenia
Investigations
Rare: Increased liver enzymes (ALAT, ASAT)

4.9 Overdose

In connection with Amlodipine:

In humans experience with intentional overdose is limited.

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

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, hypoglycemia. To date a few cases of overdose with bisoprolol. In hypertensive and/or ischemic heart disease patients have been reported: Bradycardia and/or hypotension was 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: i.v. diuretics, positive inotropic agents, vasodilating agents should be administered.
Bronchospasm: Bronchodilator therapy such as isoprenaline, beta 2-sympathomimetic drugs and/or aminophylline should be administered. Hypoglycaemia: i.v. glucose should be administered.
Hypoglycaemia: i.v. glucose should be administered.

5. Pharmacological properties

5.1 Mechanism of action

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 anti-hypertensive 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 ischemic burden by the following two actions:
1) 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.
2) The mechanism of action of amlodipine also probably involves
dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).
Mechanism of action of Bisoprolol: Bisoprolol is a potent, highly β-1 selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilizing activity. It only shows low affinity to the β 2-receptor of the smooth muscles of bronchi and vessels as well as to the beta-2receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta 2-mediated metabolic effects. Its β-1 selectivity extends beyond the therapeutic dose range. Bisoprolol has no explicit negative inotropic effect. Bisoprolol has its maximal effect 3-4 hours after oral administration. The plasma elimination half-life (10-12 hours) provides 24 hours

efficacy following a once daily dosage. It usually exerts its maximal antihypertensive effect after 2 weeks. In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Antihypertensive effect of betablockers is among others due to decrease of renin activity.

5.2 Pharmacodynamics properties

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 me, 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.

5.3 Pharmacokinetic properties

Amlodipine:

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed will 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 211/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 metabolized 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 Fumarate:

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 metabolized by the liver to inactive metabolites, which are then excreted by the kidneys. The

remaining 50% is excreted by the kidneys in unmetabolized 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 151/h. The elimination half-life in plasma is 10-12 hours. The kinetics of bisoprolol are linear and independent of age.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

The results of the toxicology studies are described:
Combination of Amlodipine and Bisoprolol: The impurity Amlodipine-2 was tested in sub chronic toxicity studies (1 study of 7 days and 2 studies of 28 days duration) and in genotoxicity studies (Ames test and in-vitro mammalian chromosome aberration test in Chinese Hamster V79 cells). An oral doserange-finding study was performed in Wistar rats at doses of 5, 20 and 80 mg/kg/day (1 : 1 ratio of Amlodipine : Bisoprolol) for 7 days to allow dose setting for a 28 day sub chronic toxicity study. 80 mg/kg/day caused mortality in male (3/5) and female (3/5) animals. The Amlodipine Bisoprolol combination caused clinical signs (decreased body lone, piloerection, swollen abdomen, spots on the skin of forelimbs and mouth and lack of stools in the bedding material) at 80 mg/kg/day. The body weight development and food consumption were dose-dependently reduced at doses of > 20 mg/kg/day. The Amlodipine-Bisoprolol combination induced changes in the gastro-intestinal tract (dilated stomach, duodenum and jejunum, and few stools in the ileum and large intestines) at 80 mg/kg/day and in one female animal at 20 mg/kg/day. Several organ weights were lower at doses of > 20 mg/kg/day. Adrenal weights were enlarged at 80 mg/kg/day. Based on the results of this study, doses of 5, 10 and 20 mg/kg/day of the Amlodipine-Bisoprolol combination (ratio of 1: 1) were chosen for the 28 days study. An oral sub chronic toxicity study was performed in Wistar rats at doses of 5/5, 10/10 and 20/20 mg/kg/day (Amlodipine: Bisoprolol at a 1 : 1 ratio) for 28 days.
There was no mortality, and clinical symptoms were decreased activity and piloerection in one female animal at 20 mg/kg/day. Body weight and food consumption were decreased at 20 mg/kg/day. No changes in clinical chemistry. hematology or urinalysis were observed. Gross pathology demonstrated increase in heart weight at all doses (> 5 mg/kg/day,) and decreases in accessory sexual glands (seminal vesicles and prostate) at 20 mg/kg/day. Intestinal dilation was observed at 20 mg/kg/day. The NOAEL was 10 mg/kg/day. A second oral subchronic toxicity study was performed in Wistar rats at the same doses of 5/5, 10/10 and 20120 mg/kg/day (Amlodipine: Bisoprolol at a 1 : 1 ratio)for 28days, but the combination product was spiked with (impurity Amlodipine 2, 3 %). Mortality occurred in two animals at 20 mg/kg/day, and preterminally increased respiratory rate, piloerection, decreased activity and swollen abdomen were observed; mortality at this dose seemed to be caused by circulatory disturbances. In surviving animals at 20 mg/kg/day, decreased activity and piloerection were found. Body weight was not altered, and food consumption was decreased at 20 mg/kg/day. No changes in clinical chemistry and hematology were observed. Urinalysis revealed a higher urine volume at 20 mg/kg/day. Gross pathology demonstrated increases in heart weight at doses of> 10 mg/kg/day and decreases in in accessory sexual glands (seminal vesicles with coagulating gland) at 20 mg/kg/day. Intestinal dilation was observed a120 mg/kg/day. The NOAEL was 10 mg/kg/day. In conclusion, the toxicological effects of the Amlodipine-Bisoprolol combination with and without spiked impurity

were similar. An Ames test was performed in Salmonella typhimurium and in Escherichia coli with the Amlodipine Bisoprolol combination spiked with or without impurity 1(3 %) up to 1581 µg/pate in the absence and presence of activated rat liver S9.
Both combinations with and without the spiked impurity did not induce gene rotations by base pair changes or frames/lifts. A chromosome aberration test in cultured Chinese Hamster Lung cells was performed with the Amlodipine-Bisoprolol combination spiked with or without impurity (3 %) up to39 µg/ml in the absence and presence of metabolic activation. The combination tested with or without the impurity did not induce structural chromosomal aberrations, and, therefore, is considered to be anticlastogenic. In conclusion, Amlodipine-2 was demonstrated to be non-mutagenic in the Ames test and non-genotoxic in the mammalian chromosome aberration test. In the 28 day sub chronic toxicity study performed in Wistar rats, tne impurity did not show additional toxicity compared to the Amlodipine- Biramlo 5 mg/5 mg; 5 mg/10 mg; 10 mg/5 mg; 10 mg/10 mg Tablet ten DE/H/3907/01-04/DC Public Assessment Report Page B/15 Bisoprolol combination tested alone. Impurity Amlodipine-2 is therefore qualified from a toxicological point of view.

7. Description

Bisosafe AM 2.5 is supplied for oral administration as film coated tablet of Bisoprolol Fumarate and Amlodipine Besilate. Each film coated tablet of Bisosafe AM 2.5 contains Bisoprolol Fumarate 2.5 mg and Amlodipine Besilate equivalent to Amlodipine 5 mg.

Bisosafe AM 5 is supplied for oral administration as film coated tablet of Bisoprolol Fumarate and Amlodipine Besilate. Each film coated tablet of Bisosafe AM 5 contains Bisoprolol Fumarate 5 mg and Amlodipine Besilate equivalent to Amlodipine 5 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities:

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition & handling instructions

Refer Pack

9. Patient Counselling Information:

Bisoprolol/Amlodipine FDC therapy is associated with significant BP improvements in patients with essential hypertension following monotherapy failure.

10. Manufactured by:

Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 & 111 to 116
First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.
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11. Details of permission or licence number with date
Refer Pack for Permission/License details.

12. Date of revision
Version 2.0, dated 29-Sep-25

For Product Complaints/Adverse events or Queries please write to
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