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

CORBIS AM

1. GENERIC NAME

Bisoprolol and Amlodipine Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CORBIS AM 2.5

Each film coated tablet contains:

Bisoprolol Fumarate I.P. ……2.5 mg

Amlodipine Besylate I.P. equivalent to Amlodipine ….5 mg

Colour: Titanium dioxide I.P.

The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Talc, Polyvinyl Alcohol and Polyethylene Glycol.

CORBIS AM 5

Each film coated tablet contains:

Bisoprolol Fumarate I.P. ……5 mg

Amlodipine Besylate I.P. equivalent to Amlodipine …….5 mg

Colour: Titanium dioxide I.P. & Lake of Sunset Yellow

The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Ethyl Cellulose, Triacetin, Sunset Yellow FCF.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Film Coated Tablet

Strength: Bisoprolol Fumarate – 2.5mg/5 mg, Amlodipine Besylate – 5mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

CORBIS AM 2.5

It is indicated for the treatment of mild to moderate hypertension in adults.

CORBIS AM 5

It is indicated for the treatment of hypertension.

4.2 Posology and Method of Administration

As directed by the Physician.

4.3 Contraindications

Bisoprolol and Amlodipine is contraindicated in chronic heart failure patients with:

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- Cardiogenic shock
- Second or third degree AV block
- Sick sinus syndrome
- Sinoatrial block
- Symptomatic bradycardia
- Symptomatic hypotension
- Severe bronchial asthma
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- Untreated phaeochromocytoma
- Metabolic acidosis
- Hypersensitivity to bisoprolol dihydropyridine derivatives, amlodipine or to any of the excipients listed.
- 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.

4.4 Special Warnings and Precautions for Use

Bisoprolol Fumarate

Bisoprolol must be used with caution in:

- Bronchospasm (bronchial asthma, obstructive airways diseases)
- Diabetes mellitus with large fluctuations in blood glucose values; Symptoms of hypoglycaemia can be masked
- Strict fasting
- Ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment does not always yield the expected therapeutic effect.
- First degree AV block
- Prinzmetal's angina: Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- Peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- General anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the postoperative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist 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.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhytmic drugs and with centrally acting antihypertensive drugs is generally not recommended.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, CORBIS may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). 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 $beta_2$-stimulants may have to be increased.

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.

In patients with phaeochromocytoma bisoprolol must not be administered until after alphareceptor blockade.

Under treatment with bisoprolol the symptoms of a thyreotoxicosis may be masked.

Amlodipine Besylate

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 reported 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.

Patients with hepatic impairment

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 initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

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 dialysable.

4.5 Drugs Interactions

Bisoprolol Fumarate

Combinations not recommended

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to betablocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors 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.

β-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. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-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.

Amlodipine Besylate

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, 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.

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.

Mechanistic Target of Rapamycin (mTOR) Inhibitors mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

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.

4.6 Use in Special Populations (Such As Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Bisoprolol Fumarate

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/new-born. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and new-born infant. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The new-born 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 this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

Amlodipine Besylate

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

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. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of 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 reported rat study, adverse effects were found on male fertility.

4.7 Effects on Ability to Drive and Use Machines

Bisoprolol Fumarate

In a reported study with coronary heart disease patients bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

Amlodipine Besylate

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. Caution is recommended especially at the start of treatment.

4.8 Undesirable Effects

Bisoprolol Fumarate

The following definitions apply to the frequency terminology used hereafter:

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 available data)

Cardiac disorders:	
Very common:	bradycardia.
Common:	worsening of heart failure.
Uncommon:	AV-conduction disturbances.
Investigations:	
Rare:	increased triglycerides, increased liver enzymes (ALAT, ASAT).
Nervous system disorders:	
Common:	dizziness, headache.
Rare:	syncope
Eye disorders:	
Rare:	reduced tear flow (to be considered if the patient uses lenses).
Very rare:	conjunctivitis.
Ear and labyrinth disorders:	
Rare	hearing disorders.
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.

Rare:	allergic rhinitis.
Gastrointestinal disorders:	
Common:	gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.
Skin and subcutaneous tissue disorders:	
Rare:	hypersensitivity reactions (itching, flush, rash).
Very rare:	Alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash
Musculoskeletal and connective tissue disorders:	
Uncommon:	muscular weakness and cramps.
Vascular disorders:	
Common:	feeling of coldness or numbness in the extremities, hypotension.
Uncommon:	orthostatic hypotension.
General disorders:	
Common:	asthenia, fatigue.
Hepatobiliary disorders:	
Rare:	hepatitis.
Reproductive system and breast disorders:	
Rare:	potency disorders, erectile dysfunction
Psychiatric disorders:	
Uncommon:	sleep disorders, depression.
Rare:	nightmares, hallucinations.

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

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Bisoprolol Fumarate

Symptoms

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported**.** In general, 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 (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore, it is mandatory to initiate the treatment of these patients with a gradual up titration according to the scheme given in Posology and method of administration.

Management

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 pharmacologic 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 transvenous cardiac pacemaker insertion.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta$_2$sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Amlodipine Besylate

In human's 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of Action

Bisoprolol Fumarate

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$selectivity extends beyond the therapeutic dose range.

Amlodipine Besylate

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.

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 ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

5.2. Pharmacodynamic Properties

Bisoprolol Fumarate

Pharmacotherapeutic group: Beta blocking agents, selective

ATC Code: C07AB07

Clinical efficacy and safety:

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction $\leq$35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status

according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total reported study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months' treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months' treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at reported study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The reported study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

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.

Amlodipine Besylate

Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

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.

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled reported study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, betablockers, diuretics and aspirin, for 2 years. The key efficacy results are presented here. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Incidence of significant clinical outcomes for CAMELOT					
	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24

vascular disease					
Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.					

Use in patients with heart failure

Haemodynamic reported studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A reported placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a reported follow-up, long term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine had no effect on total cardiovascular mortality. In this same population Amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomised double-blind morbidity-mortality reported study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipinebased therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Use in children (aged 6 years and older)

In a reported study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

5.3 Pharmacokinetic Properties

Bisoprolol Fumarate

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.
Distribution

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

Biotransformation 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 an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24-hour effect after dosing once daily.

Linearity

The kinetics of bisoprolol are linear and independent of age.

Special population

Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

Amlodipine Besylate

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. *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 4060%.

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 halflife in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

A reported population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

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

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Bisoprolol Fumarate

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

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

Amlodipine Besylate

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 of rats 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/m^2 basis). In another reported 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

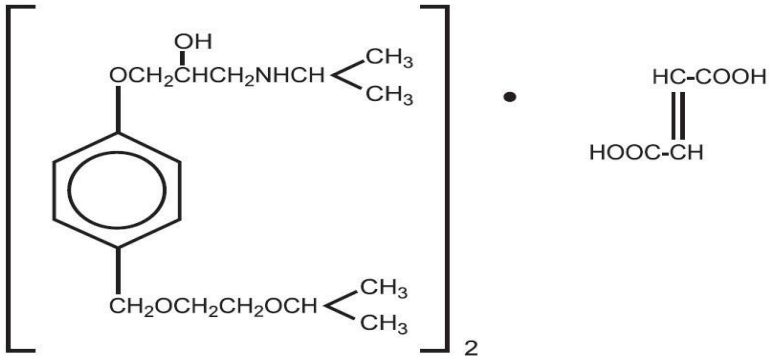
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 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.)

7. DESCRIPTION

Bisoprolol and Amlodipine Tablets are indicated for the treatment of hypertension.

Bisoprolol Fumarate

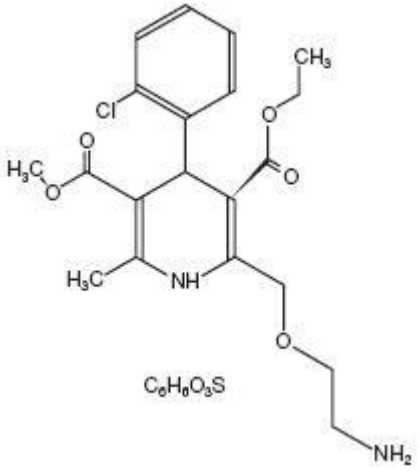
Bisoprolol Fumarate is chemically described as 2-propanol,1-[4-[[2-(1-methylethoxy) ethoxy)methyl]phenoxy]-3-[(1-methylethyl)amino]-,(±)-,(E)-2-butenedioate. Its molecular formula is $(C_{18}H_{31}NO_4)_2 \bullet C_4H_4O_4$ and it has a molecular weight of 766.97. Its structural formula is:



Bisoprolol fumarate is a white crystalline powder and very soluble in water and in methanol; freely soluble in chloroform, in glacial acetic acid, and in alcohol; slightly soluble in acetone and in ethyl acetate.

Amlodipine Besylate

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene-sulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white or almost white powder with a molecular weight of 567.1. it is freely soluble in methanol; sparingly soluble in ethanol (95 percent); slightly soluble in 2-propanol and in water.

CORBIS AM 2.5

Bisoprolol and Amlodipine Tablets are white coloured, circular shaped, film coated tablet with plain on both sides. The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Talc, Polyvinyl Alcohol and Polyethylene Glycol.

CORBIS AM 5

Bisoprolol and Amlodipine Tablets are beige coloured, circular shaped, film coated tablet with plain on both sides. The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Ethyl Cellulose, Triacetin, Sunset Yellow FCF.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not Available

8.2 Shelf life

Do not use later than date of expiry.

8.3 Packaging information

CORBIS AM is available in blister strip of 10 tablets.

8.4 Storage and Handing Instructions

- Store below 30^{o}C. Protect from light and moisture.
- Keep out of the reach of children.

9. PATIENT COUNSELLING INFORMATION

CORBIS AM

(Bisoprolol and Amlodipine Tablets)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1 What CORBIS AM is and what it is used for

The active substance in CORBIS AM is combination of Bisoprolol and Amlodipine. Bisoprolol belongs to a group of medicines called beta-blockers. These medicines work by affecting the body`s response to some nerve impulses, especially in the heart. As a result, Bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body.

Amlodipine Besylate belongs to a group of medicines called calcium antagonists. In patients with high blood pressure this medicine works by relaxing blood vessels, so that blood passes through them more easily.

Bisoprolol/amlodipine is used for the treatment of mild to moderate hypertension in adults.

9.2 What you need to know before you take

Do not take CORBIS AM if one of the following conditions applies to you:

- allergy (hypersensitivity) to CORBIS AM or to any of the other ingredients
- severe asthma severe blood circulation problems in your limbs (such as Raynaud's syndrome), which may cause your fingers and toes to tingle or turn pale or blue
- untreated phaeochromocytoma, which is a rare tumour of the adrenal gland
- metabolic acidosis, which is a condition when there is too much acid in the blood.

Do not take CORBIS AM if you have one of the following heart problems:

- acute heart failure
- worsening heart failure requiring injection of medicines into a vein, that increase the force of contraction of the heart
- slow heart rate
- low blood pressure
- certain heart conditions causing a very slow heart rate or irregular heartbeat
- cardiogenic shock, which is an acute serious heart condition causing low blood pressure and
- circulatory failure.
- If you have severe low blood pressure (hypotension).
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.

Warnings and precautions

If you have any of the following conditions tell your doctor before taking CORBIS AM; he or she may want to take special care (for example give additional treatment or perform more frequent checks):

- diabetes
- strict fasting
- certain heart diseases such as disturbances in heart rhythm, or severe chest pain at rest
- (Prinzmetal's angina)
- kidney or liver problems
- less severe blood circulation problems in your limbs
- chronic lung disease or less severe asthma
- history of a scaly skin rash (psoriasis)

- tumour of the adrenal gland (phaeochromocytoma)
- thyroid disorder
- Recent heart attack
- Heart failure
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased.

In addition, tell your doctor if you are going to have:

- desensitization therapy (for example for the prevention of hay fever), because CORBIS AM may make it more likely that you experience an allergic reaction, or such reaction may be more severe
- anaesthesia (for example for surgery), because CORBIS AM may influence how your body reacts to this situation.

If you have chronic lung disease or less severe asthma please inform your doctor immediately if you start to experience new difficulties in breathing, cough, wheezing after exercise, etc. when using CORBIS AM.

Children and adolescents

CORBIS AM is not recommended for use in children or Adolescents

Other medicines and CORBIS AM

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take the following medicines with CORBIS AM without special advice from your doctor:

- certain medicines used to treat irregular or abnormal heartbeat (Class I antiarrhythmic medicines such as quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone)
- certain medicines used to treat high blood pressure, angina pectoris or irregular heartbeat (calcium antagonists such as verapamil and diltiazem)
- certain medicines used to treat high blood pressure such as clonidine, methyldopa, moxonodine, rilmenidine. However, do not stop taking these medicines without checking with your doctor first.

Check with your doctor before taking the following medicines with CORBIS AM; your doctor may need to check your condition more frequently:

- certain medicines used to treat irregular or abnormal heartbeat (Class III antiarrhythmic medicines such as amiodarone)
- beta-blockers applied locally (such as timolol eye drops for glaucoma treatment)
- certain medicines used to treat for example Alzheimer's disease or glaucoma (parasympathomimetics such as tacrine or carbachol) or medicines that are used to treat acute heart problems (sympathomimetics such as isoprenaline and dobutamine)
- antidiabetic medicines including insulin
- anaesthetic agents (for example during surgery)
- digitalis, used to treat heart failure

- non-steroidal anti-inflammatory medicines (NSAIDs) used to treat arthritis, pain or inflammation (for example ibuprofen or diclofenac)
- any medicine, which can lower blood pressure as a desired or undesired effect such as antihypertensives, certain medicines for depression (tricyclic antidepressants such as imipramine or amitriptyline), certain medicines used to treat epilepsy or during anaesthesia (barbiturates such as phenobarbital), or certain medicines to treat mental illness characterized by a loss of contact with reality (phenothiazines such as levomepromazine)
- mefloquine, used for prevention or treatment of malaria
- depression treatment medicines called monoamine oxidase inhibitors (except MAO-B inhibitors) such as moclobemide.

CORBIS AM may affect or be affected by other medicines, such as:

- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St. John's Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities) tacrolimus, sirolimus, temsirolimus, and everolimus (medicines used to alter the way your immune system works)
- simvastatin (cholesterol lowering medicine)
- cyclosporine (an immunosuppressant)

CORBIS AM with food and drink

Grapefruit juice and grapefruit should not be consumed by people who are taking Amlodipine Besylate. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Amlodipine Besylate.

Pregnancy and breast-feeding

Pregnancy

There is a risk that use of CORBIS AM during pregnancy may harm the baby. If you are pregnant or planning to become pregnant, tell your doctor. He or she will decide whether you can take CORBIS AM during pregnancy.

Breast-feeding

Amlodipine has been shown to pass into breast milk in small amounts. If you are breastfeeding or about to start breast-feeding, you must tell your doctor before taking Amlodipine Besylate containing drug. Ask your doctor or pharmacist for advice before taking CORBIS AM.

Driving and using machines

Your ability to drive or use machinery may be affected depending on how well you tolerate the medicine. Please be especially cautious at the start of treatment, when the dose is increased or the medication is changed, as well as in combination with alcohol.

9.3 How to take CORBIS AM

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Treatment with CORBIS AM requires regular monitoring by your doctor. This is particularly necessary at the start of treatment, during dose increase and when you stop treatment. Take the tablet with some water in the morning, with or without food. Do not crush or chew the tablet.

Treatment with CORBIS AM is usually long-term.

Dosage: As directed by the Physician.

If you take more CORBIS AM than you should

If you have taken more CORBIS AM tablets than you should, tell your doctor immediately. Your doctor will decide what measures are necessary. Symptoms of an overdose may include slowed heart rate, severe difficulty in breathing, feeling dizzy, or trembling (due to decreased blood sugar).

Seek immediate medical attention if you take too many CORBIS AM tablets.

If you forget to take CORBIS AM

Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking CORBIS AM

Never stop taking CORBIS AM unless on your doctor's advice. Otherwise your condition could become much

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly.

The most serious side effects are related to the heart function:

- Slowing of heart rate (may affect more than 1 in 10 people)
- Worsening of heart failure (may affect up to 1 in 10 people)
- Slow or irregular heartbeat (may affect up to 1 in 100 people)
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

If you feel dizzy or weak, or have breathing difficulties please contact your doctor as soon as possible.

Further side effects are listed below according to how frequently they may occur:

Common (may affect up to 1 in 10 people):

- tiredness, feeling weak, dizziness, headache, sleepiness (especially at the beginning of treatment)
- feeling of coldness
- low blood pressure
- stomach or intestine problems such as abdominal pain, feeling sick (nausea)
- Altered bowel habits, indigestion, vomiting, diarrhoea, or constipation.
- Palpitations (awareness of your heart beat), flushing
- Visual disturbances, double vision
- Muscle cramps
- Ankle swelling

Uncommon (may affect up to 1 in 100 people):

- dizziness when standing up
- breathing problems in patients with asthma or chronic lung disease
- muscle weakness,
- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting
- Numbness or tingling sensation in your limbs, loss of pain sensation
- Ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Cough
- Dry mouth
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Pain, feeling unwell
- Joint or muscle pain, back pain
- Weight increase or decrease

Rare (may affect up to 1 in 1,000 people):

- Hearing problems
- Reduced tear flow
- Confusion
- Inflammation of the liver which can cause yellowing of the skin or whites of the eyes
- Certain blood test results for liver function or fat levels differing from normal
- Allergy-like reactions such as itching, flush, rash
- Impaired erection
- Nightmares, hallucinations
- Fainting.

Very rare (may affect up to 1 in 10,000 people):

- Irritation and redness of the eye (conjunctivitis)
- Hair loss

- Appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash.
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause muscular weakness, tingling or numbness
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin
- (jaundice), liver enzyme increase which may have an effect on some medical tests • Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store CORBIS AM

Store below 30ºC. Protect from light and moisture.

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

CORBIS AM 2.5

In Each film coated tablet Active ingredients are

Bisoprolol Fumarate 2.5 mg and Amlodipine Besylate 5 mg

The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Talc, Polyvinyl Alcohol and Polyethylene Glycol.

CORBIS AM 5

In Each film coated tablet Active ingredients are

Bisoprolol Fumarate 5 mg and Amlodipine Besylate 5 mg

The excipients used are Colloidal Silicon dioxide, Sodium Starch Glycolate, Magnesium Stearate, Microcrystalline cellulose, Isopropyl Alcohol, Methylene chloride, Hypromellose, Titanium Dioxide, Ethyl Cellulose, Triacetin, Sunset Yellow FCF.

CORBIS AM is available in blister strip of 10 tablets.

10. DETAILS OF MANUFACTURER

Manufactured in India by:

Ordain Health Care Global Pvt. Ltd.

532, Uthiramerur Road,

Melavalampettal, Karunguzhi – 603 303,

Kanchipuram District, Tamil Nadu

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. TN00003296 issued on 18.02.2020.

12. DATE OF REVISION

APR-2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ CORBIS AM 2.5/5mg, 5/5 mg/APR-21/03/PI