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AMLOPRES AT Tablets (Amlodipine + Atenolol)

Qualitative And Quantitative Composition

AMLOPRES-AT 50
Each tablet contains:
Amlodipine Besylate equivalent to Amlodipine.....5 mg
Atenolol.....50 mg
AMLOPRES-AT 25
Each tablet contains:
Amlodipine Besylate equivalent to Amlodipine .....5 mg
Atenolol.....25 mg

Dosage Form And Strength

Amlodipine 5 mg and Atenolol 50 mg Oral Tablets
Amlodipine 5mg and Atenolol 25 mg Oral Tablets

Clinical Particulars

▶ Therapeutic Indications

Essential Hypertension
Angina Pectoris

▶ Posology and Method of Administration

The recommended dosage is one tablet of Amlopres-AT daily. If necessary, the dosage may be increased to two tablets daily. The dosage however should be individualized.
Special Populations
Patients with Renal Impairment
Dosage of AMLOPRES-AT should be adjusted in cases of severe impairment of renal function. Dosage of atenolol should not exceed 50 mg/day when creatinine clearance is 15-35 ml/min/1.73 m^2. While in patients with creatinine clearance <15 ml/min/1.73 m^2, the maximum dosage of atenolol should be 25 mg/day.
Patients with Hepatic Impairment
The recommended initial dose in patients with hepatic impairment is half tablet of AMLOPRES-AT.
Elderly Patients (65 years or above)
Dose selection for an elderly patient should be cautious, usually starting at half tablet of AMLOPRES-AT.

▶ Contraindications

Hypersensitivity to either component, cardiogenic shock, uncontrolled heart failure, sick sinus syndrome, second-or third-degree heart block, untreated phaeochromocytoma, metabolic acidosis, bradycardia (<45 bpm), hypotension, and severe peripheral arterial circulatory disturbances.

▶ Special Warnings and Precautions for Use

General

Patients already on a beta-blocker must be evaluated carefully before AMLOPRES-AT Tablets are administered. Initial and subsequent dosages can be adjusted downward depending on clinical observations, including pulse and blood pressure. The combination may aggravate peripheral arterial circulatory disorders.

Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina and/or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of AMLOPRES-AT Tablets, particularly in patients with severe obstructive coronary artery disease.

Patients with Hepatic Failure

Titrate slowly when administering AMLOPRES-AT Tablets to patients with severe hepatic impairment.

Elderly Patients

In the elderly, increase of the dosage should be done carefully.

Patients with Renal Impairment

AMLOPRES-AT Tablets should be used with caution in impaired renal function.

Cardiac Failure

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure.

In patients with acute myocardial infarction, cardiac failure that is not promptly and effectively controlled by 80 mg of IV furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, AMLOPRES-AT Tablets should be withdrawn.

Concomitant Use of Calcium Channel Blockers

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible.

Bronchospastic Diseases

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative $beta_1$ selectivity, however, this combination may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. The lowest possible dose should be used.

Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anaesthesia and surgical procedures.

Diabetes and Hypoglycaemia

AMLOPRES-AT Tablets should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as

dizziness and sweating may not be significantly affected. At recommended doses, atenolol does not potentiate insulin-induced hypoglycaemia and, unlike non-selective beta-blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta-blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis and from whom atenolol therapy is to be withdrawn should be monitored closely.

Untreated Pheochromocytoma

AMLOPRES-AT Tablets should not be given to patients with untreated pheochromocytoma.

Pregnancy and Foetal Injury

AMLOPRES-AT Tablets can cause foetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of the combination, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of the combination in the first trimester and the possibility of foetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

Neonates born to mothers who are receiving the combination at parturition or breast-feeding may be at risk for hypoglycaemia and bradycardia. Caution should be exercised when AMLOPRES-AT Tablets are administered during pregnancy or to a woman who is breastfeeding.

Atenolol has been shown to produce a dose-related increase in embryo/foetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.[1] Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose[2] ([1] based on the maximum dose of 100 mg/day in a 50 kg patient; [2] based on the maximum dose of 100 mg/day in a 50 kg patient).

▶ Drug Interactions

CYP3A4 inhibitors

Concomitant use of AMLOPRES-AT Tablets 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 pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may, thus, be required.

CYP3A4 Inducers

The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may give a lower plasma concentration of AMLOPRES-AT Tablets. AMLOPRES-AT Tablets should be used with caution together with CYP3A4 inducers.

Administration of AMLOPRES-AT Tablets 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 hyperkalaemia after administration of verapamil and IV dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of AMLOPRES-AT Tablets be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with AMLOPRES-AT Tablets.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with AMLOPRES-AT Tablets but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of AMLOPRES-AT Tablets 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 the combination 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 the combination, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Limit the dose of simvastatin in patients on AMLOPRES-AT Tablets.

Catecholamine-depleting Drugs

Catecholamine-depleting drugs (e.g. reserpine) may have an additive effect when given with the combination. Patients treated with AMLOPRES-AT Tablets plus a catecholamine depletor should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium Channel Blockers

Calcium channel blockers may also have an additive effect when given with atenolol.

Disopyramide

Disopyramide is a type I antiarrhythmic drug with potent negative inotropic and chronotropic effects. Disopyramide has been associated with severe bradycardia, asystole and heart failure when administered with beta-blockers.

Amiodarone

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta-blockers.

Beta-blockers

Beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If the two drugs are co-administered, AMLOPRES-AT Tablets should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by the combination therapy, the introduction of the combination should be delayed for several days after clonidine administration has stopped.

Prostaglandin Synthase-inhibiting Drugs

Concomitant use of prostaglandin synthase inhibiting drugs, e.g. indomethacin, may decrease the hypotensive effects of AMLOPRES-AT Tablets.

Aspirin

Information on concurrent usage of the combination and aspirin is limited. Data from several studies, i.e. TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and the combination in the acute myocardial infarction setting.

Digitalis Glycosides

Both digitalis glycosides and the combination slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

While taking AMLOPRES-AT Tablets, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental or diagnostic or therapeutic. Such

patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.
Caution must be exercised when using anaesthetic agents with AMLOPRES-AT Tablets. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of the combination with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

▶ Use in Special Population

Renal Impairment
The dosage of AMLOPRES-AT Tablets should be reduced in patients with a creatinine clearance <35 ml/min/1.73 m^2.
Hepatic Impairment
Caution may be necessary in the use of the combination in patients with severe liver damage because of the prolongation of the elimination half-life of amlodipine.
Pregnancy
The combination should be used during pregnancy only if the expected benefit outweighs the potential foetal risk.
Lactation
The combination should not be used by lactating women. If its use is considered necessary, breastfeeding should be stopped.
Pediatric Use
Safety and effectiveness of this combination has not been evaluated in paediatric patients.
Geriatric Use
Amlodipine
Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required.
Atenolol
Hypertension and Angina Pectoris due to Coronary Atherosclerosis
Clinical studies of atenolol did not include sufficient number of patients aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
Acute Myocardial Infarction
Of the 8,037 patients with suspected acute myocardial infarction randomized to atenolol in the ISIS-1 trial, 33% (2,644) were 65 years of age and older. It was not possible to identify significant differences in efficacy and safety between older and younger patients; however, elderly patients with systolic blood pressure <120 mmHg seemed less likely to benefit.
In general, dose selection should be done with caution in elderly patients, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of

concomitant disease or other drug therapy.

▶ Effects on the Ability to Drive and Use Machines

Caution is recommended, especially at the start of treatment with the combination.

▶ Undesirable Effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine at doses up to 10 mg to placebo, discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue. The incidence (%) of side effects that occurred in a dose-related manner is as follows:

Adverse Events	2.5 mg (N = 275) %	5 mg (N = 296) %	10 mg (N = 268) %	Placebo (N = 520) %
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences that were not clearly dose-related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials included the following:

	Amlodipine (%) (N = 1,730)	Placebo (%) (N = 1,250)
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug- and dose-related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Event	Amlodipine		Placebo	
	Male (%) (N = 1,218)	Female (%) (N = 512)	Male (%) (N = 914)	Female (%) (N = 336)
Oedema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischaemia, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: Hypoesthesia, neuropathy peripheral, paraesthesia, tremor, vertigo.

Gastrointestinal: Anorexia, constipation, dysphagia, diarrhoea, flatulence, pancreatitis, vomiting, gingival hypertrophy.

General: Allergic reaction, asthenia**, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: Arthralgia, arthrosis, muscle cramps**, myalgia.

Psychiatric: Sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: Dyspnoea**, epistaxis.

Skin and Appendages: Angio-oedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.

Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: Micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hyperglycaemia, thirst.

Haemopoietic: Leucopenia, purpura, thrombocytopaenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple-dose studies.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

In the CAMELOT and PREVENT studies, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral oedema.

Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynaecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in

association with use of amlodipine. Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Atenolol

Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patients (US studies) or elicited, e.g. by a checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol- and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of atenolol and placebo is similar, a causal relationship to atenolol is uncertain.

	Volunteered (US Studies)		Total – Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
Cardiovascular				
Bardycardia	3	0	3	0
Cold extremities	0	0.5	12	5
Postural hypotension	2	1	4	5
Leg pain	0	0.5	3	1
Central Nervous System/ Neuromuscular				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
Gastrointestinal				
Diarrhoea	2	0	3	2
Nausea	4	1	3	1
Respiratory				
Wheeziness	0	0	3	3
Dyspnoea	0.6	1	6	4

Acute Myocardial Infarction

In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta-blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The

reported frequency of these and other events occurring during these investigations is given in the following table.

Summary of adverse drug reactions from clinical studies

In a study of 477 patients, the following adverse events were reported during either IV and/or oral atenolol administration:

	Conventional Therapy plus Atenolol (n = 244)	Conventional Therapy Alone (n = 233)
Bradycardia	43 (18%)	24 (10%)
Hypotension	60 (25%)	34 (15%)
Bronchospasm	3 (1.2%)	2 (0.9%)
Heart failure	46 (19%)	56 (24%)
Heart block	11 (4.5%)	10 (4.3%)
BBB+Major Axis deviation	16 (6.6%)	28 (12%)
Supraventricular tachycardia	28 (11.5%)	45 (19%)
Atrial fibrillation	12 (5%)	29 (11%)
Atrial flutter	4 (1.6%)	7 (3%)
Ventricular tachycardia	39 (16%)	52 (22%)
Cardiac re-infarction	0 (0%)	6 (2.6%)
Total cardiac arrests	4 (1.6%)	16 (6.9%)
No fatal cardiac arrests	4 (1.6%)	12 (5.1%)
Deaths	7 (2.9%)	16 (6.9%)
Cardiogenic shocks	1 (0.4%)	4 (1.7%)
Development of ventricular septal defect	0 (0%)	2 (0.9%)
Development of mitral regurgitation	0 (0%)	2 (0.9%)
Renal failure	1 (0.4%)	0 (0%)
Pulmonary emboli	3 (1.2%)	0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive atenolol treatment, the dosage of IV and subsequent oral atenolol was either discontinued or reduced for the following reasons:

Reasons for Reduced Dosage		
	IV Atenolol Reduced Dose (<5 mg)*	Oral Partial Dose

Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic shock	4	(0.04%)	35	(0.44%)
Re-infarction	0	(0%)	5	(0.06%)
Cardiac arrest	5	(0.06%)	28	(0.34%)
Heart block (>first-degree)	5	(0.06%)	143	(1.7%)
Cardiac failure	1	(0.01%)	233	(2.9%)
Arrhythmias	3	(0.04%)	22	(0.27%)
Bronchospasm	1	(0.01%)	50	(0.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

▶ Adverse drug reactions from spontaneous reports and literature cases - post-marketing experience

During postmarketing experience with atenolol, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension, which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychses, purpura, reversible alopecia, thrombocytopenia, visual disturbance, sick sinus syndrome, and dry mouth. Atenolol, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome and Raynaud's phenomenon.

▶ Potential Adverse Effects

In addition, a range of adverse effects has been reported with other beta-adrenergic blocking agents, and may be considered potential adverse of atenolol.

Haematologic

Agranulocytosis.

Allergic

Fever, combined with aching and sore throat laryngospasm and respiratory distress.

Central Nervous System

Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation of time and place; short-time memory loss; emotional lability with slightly clouded sensorium; and decreased performance on neuropschyometrics.

Gastrointestinal

Mesentric arterial thrombosis, ischaemic colitis.

Other

Erythematous rash.

Miscellaneous

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic-blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuity of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol

reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

▶ Overdose

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and, possibly, a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein-bound, haemodialysis is not likely to be of benefit.

Atenolol

Overdosage with atenolol has been reported, with patients surviving acute doses as high as 5 g. One death was reported in a man have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic-blocking agent and which might also be expected in atenolol overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycaemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. Atenolol can be removed from the general circulation by haemodialysis. Other treatment modalities should be employed at the physician's discretion and may include the following:

Bradycardia

IV atropine. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

Heart Block (Second- or Third-degree)

Isoproterenol or transvenous cardiac pacemaker.

Cardiac Failure

Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

Hypotension

Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

Bronchospasm

A $beta_2$-stimulant such as isoproterenol or terbutaline and/or aminophylline.

Hypoglycaemia

IV glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for

applying cardiac and respiratory support.

Pharmacological Properties

Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:
Exertional Angina: In patients with exertional angina, Amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.
Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of Amlodipine in vasospastic (Prinzmetal's or variant) angina.
Atenolol is a beta1-selective (cardio-selective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, Atenolol inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature

Pharmacodynamic Properties

Amlodipine
Haemodynamics
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous (IV) administration of amlodipine decreases arterial blood pressure and increases heart rate in haemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
With chronic once-daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pre-treatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater

response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta-blockers to humans. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.
Electrophysiologic Effects
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In patients with chronic stable angina, IV administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of atrioventricular) blocks.
Atenolol
In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by:
(1) reduction in resting and exercise heart rate and cardiac output,
(2) reduction of systolic and diastolic blood pressure at rest and on exercise,
(3) inhibition of isoproterenol induced tachycardia, and
(4) reduction in reflex orthostatic tachycardia.
A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within 1 hour following oral administration of a single dose. This effect is maximal at about 2–4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an IV dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10 mg IV dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration.
However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.
In normal subjects, the $beta_1$ selectivity of atenolol has been shown by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo-controlled comparison of approximately equipotent oral doses of several beta-blockers, atenolol produced a significantly smaller decrease of FEV_1 than nonselective beta-blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproerenol.

Consistent with its negative chronotropic effect due to beta-blockade of the sinoatrial (SA) node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane-stabilizing activity, and increasing the dose well beyond that producing beta-blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, atenolol, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction in blood pressure. Atenolol has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methyldopa, hydralazine and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fibre length and end diastolic pressure, particularly in patients with heart failure.

In a multicentre clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus atenolol (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of <50 bpm or systolic blood pressure <100 mmHg, or with other contraindications to beta-blockade were excluded. In each group, 38% of patients were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5 ± 2.7 hours in both groups. Patients in the atenolol group were to receive atenolol IV injection 5–10 mg given over 5 minutes plus atenolol tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either atenolol tablets 100 mg once daily or atenolol tablets 50 mg twice daily on days 2–7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first-degree atrioventricular block at entry.

During the treatment period (days 0–7), the vascular mortality rates were 3.89% in the atenolol group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, was statistically significant at the $P<0.05$ level. The absolute difference translated into a proportional reduction of 15% (3.89– 4.57/4.57 = –0.15). The 95% confidence limits were 1–27%. Most of the difference was attributed to mortality in days 0–1 (atenolol, 121 deaths; control, 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgement suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta-blockade. Indeed, the trial protocol reflected that judgement by excluding patients with blood pressure consistently below 100 mmHg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mmHg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute

myocardial infarction is unknown, as is the case with other beta-blockers in the post-infarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits, including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

Geriatric Pharmacology

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

▶ Pharmacokinetic Properties

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7–8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in area under curve (AUC) of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate-to-severe heart failure.

Pediatric Patients

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Atenolol

In humans, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the faeces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an IV dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose.

Atenolol also differs from propranolol in that only a small amount (6–16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a 4-fold interpatient variation. The elimination half-life of oral atenolol is approximately 6–7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following IV administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73 m^2.'

Nonclinical Properties

▶ Animal Toxicology and Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about twice the maximum recommended human dose. Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose3 of 10 mg/day on a mg/m2 basis).
Atenolol:
Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol.
Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Description

AMLOPRES-AT Tablets are fixed-dose combinations of amlodipine and atenolol. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Atenolol is a $beta_1$-selective (cardioselective) beta-adrenergic receptor-blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmaceutical Particulars

AMLOPRES AT 5mg/50mg
AMLOPRES AT5mg/25mg

▶ Incompatibilities

None Known

▶ Shelf-Life

AMLOPRES-AT Tablets: 3 years
Packaging Information
AMLOPRES-AT Tablets: Bottle of 30 tablets
AMLOPRES-AT Tablets: Blister pack of 15 tablets

▶ Storage and Handling Instructions

Protect from heat and light.

Patient Counseling Information

AMLOPRES -AT 5 mg/50 mg tablets
AMLOPRES -AT 5mg/25mg tablets
Read all 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, pharmacist or nurse.
- 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, pharmacist or nurse.

What is in this leaflet

1) What AMLOPRES AT is and what it is used for?

AMLOPRES AT is a type of medicine known as a calcium channel blocker (CCB). It is used to treat high blood pressure (hypertension) and a type of chest pain called angina. It can be used by itself or with other medicines to treat these conditions. High Blood Pressure (hypertension) High blood pressure comes from blood pushing too hard against your blood vessels. AMLOPRES AT relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure. Drugs that lower blood pressure lower your risk of having a stroke or heart attack. Angina is a pain or discomfort that keeps coming back when part of your heart does not get enough blood. Angina feels like a pressing or squeezing pain, usually in your chest under the breastbone. Sometimes you can feel it in your shoulders, arms, neck, jaws, or back. AMLOPRES AT can relieve this pain.

2) Who should not use AMLOPRES AT?

Do not use AMLOPRES AT if you are allergic to amlodipine (the active ingredient in AMLOPRES AT, or to the inactive ingredients. Your doctor or pharmacist can give you a list of these ingredient

3) What should I tell my doctor before taking AMLOPRES AT?

Tell your doctor about any prescription and non-prescription medicines you are taking, including natural or herbal remedies.

Tell your doctor if you:

- ever had heart disease
- ever had liver problems
- are pregnant, or plan to become pregnant.

Your doctor will decide if AMLOPRES AT is the best treatment for you.

- are breast-feeding. AMLOPRES AT passes into your milk.

4) How should I take AMLOPRES AT?

Take AMLOPRES AT once a day, with or without food.

- It may be easier to take your dose if you do it at the same time every day, such as with breakfast or

dinner, or at bedtime. Do not take more than one dose of AMLOPRES AT at a time.

• If you miss a dose, take it as soon as you remember. Do not take AMLOPRES AT if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.

• Other medicines: You can use nitroglycerin and AMLOPRES AT together. If you take nitroglycerin for angina, don't stop taking it while you are taking AMLOPRES AT.

• While you are taking AMLOPRES AT, do not stop taking your other prescription medicines, including any other blood pressure medicines, without talking to your doctor.

• If you took too much AMLOPRES AT, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

5) What should I avoid while taking AMLOPRES AT?

• Do not start any new prescription or non-prescription medicines or supplements, unless you check with your doctor first

Reporting of side effects.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

6) How *to store* AMLOPRES AT?

Keep AMLOPRES AT away from children. Store AMLOPRES AT Tablets at room temperature (between 59° and 86°F). Keep AMLOPRES AT out of the light. Do not store in the bathroom. Keep AMLOPRES AT in a dry place.

7) Contents of the pack and other information

The active substances are amlodipine and atenolol.

Each uncoated tablet contains: Amlodipine besylate equivalent to Amlodipine 5 mg and Atenolol IP 50 mg.

Each uncoated tablet contains: Amlodipine besylate equivalent to Amlodipine 5 mg and Atenolol IP 25 mg.

Details Of Manufacturer

Mfd. By Cipla Ltd.
Registered Office :
Cipla House, Peninsula Business Park,
Ganpatrao Kadam Marg
Lower Parel
Mumbai – 400 013, India

Details Of Permission Or License Number With Date

M.L.L./447/2007
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Date Of Revision

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AMLOPRES AT Tablets