AMLODANE 5 (Amlodipine Tablets 5mg)
AMLODANE 10 (Amlodipine Tablets 10mg)

COMPOSITION:
AMLODANE 5
(AMLODIPINE TABLETS 5mg)
Each uncoated tablet contains

Amlodipine Besilate BP equivalent to Amlodipine	5mg
Excipients	q.s.

AMLODANE 10
(AMLODIPINE TABLETS 10mg)
Each uncoated tablet contains

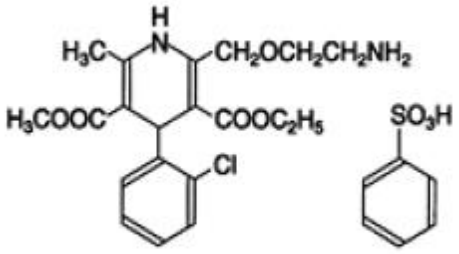
Amlodipine Besilate BP equivalent to Amlodipine	10mg
Excipients	q.s.

Excipients
Microcrystalline Cellulose
Sodium Starch Glycolate
Magnesium Stearate

PRESENTATION:
AMLODANE 5 – Blister pack of 10 Tablets & 14 Tablets
AMLODANE 10 – Blister pack of 10 Tablets & 14 Tablets

"Not all Presentations may be marketed"

PROPERTIES:
Amlodipine Besilate is the Besilate salt of Amlodipine, a long acting calcium channel blocker. Amlodipine Besilate is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ and molecular weight is 567.1



amlodipine besilate

CLINICAL PHARMACOLOGY:

Pharmacodynamic properties

Amlodipine is a calcium ion influx inhibitor (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 ischemic burden by the following two actions:

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

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction.

In patients with hypertension, once-daily dosing provides clinically significant reductions in 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 nitroglycerine 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

The effects of amlodipine on cardiovascular morbidity and mortality, the progression of coronary atherosclerosis, and carotid atherosclerosis were studied in the Prospective Randomized Evaluation of the Vascular Effects of Amlodipine Besylate Trial. This multicenter, randomized, double-blind, placebo-controlled study followed 825 patients with angiographically defined CAD for 3 years. The population included patients with previous MI (45%), percutaneous transluminal coronary angioplasty (PTCA) at baseline (42%), or history of angina (69%). The severity of CAD ranged from 1-vessel disease (45%) to 3+ vessel disease (21%). Patients with uncontrolled hypertension (diastolic blood pressure [DBP] >95 mmHg) were excluded from the study. Major cardiovascular events were adjudicated by a blinded endpoint committee. Although there were no demonstrable effects on the rate of progression of coronary artery lesions, amlodipine arrested the progression of carotid intima-media thickening. A significant reduction (-31%) was observed in amlodipine-treated patients in the combined endpoint of cardiovascular death, MI, stroke, PTCA, coronary artery bypass graft (CABG), hospitalization for unstable angina, and worsening congestive heart failure (CHF).

A significant reduction (-42%) in revascularization procedures (PTCA and CABG) was also seen in amlodipine-treated patients. Fewer hospitalizations (-33%) were seen for unstable angina in amlodipine-treated patients than in the placebo group.

CAMELOT enrolled 1997 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine besylate tablets (5 mg to 10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers, for 2 years. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, MI, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/transient ischemic attack (TIA), or peripheral vascular disease (PVD).

The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures **(see Table 1).** The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, MI, hospitalization for heart failure, stroke/TIA, or PVD did not demonstrate a significant difference between amlodipine besylate and placebo.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	Amlodipine (n=663)	Placebo (n=655)	Risk Reduction (p-value)
Composite CV Endpoint*	110 (16.6)	151 (23.1)	31% (0.003)
Hospitalization for Angina	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization	78 (11.8)	103 (15.7)	27% (0.033)

*1) Defined in CAMELOT as cardiovascular death, non-fatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or non-fatal stroke or TIA, any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD.
2) The composite cardiovascular (CV) endpoint was the primary efficacy endpoint in CAMELOT.

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

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

The primary endpoint was a composite of fatal CHD or non-fatal MI. 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 amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96 95% CI [0.89-1.02], p=0.20.

Use in Patients with Heart Failure
Hemodynamic 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 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 in patients with heart failure.

In a follow-up, long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA class III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure compared to placebo.

Pharmacokinetic properties
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
As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. The drug should therefore be administered with caution in these patients.

Elderly population
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

INDICATIONS & USES:

Hypertension
Amlodipine is indicated for the first-line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme (ACE) inhibitor.

Coronary Artery Disease
Chronic Stable Angina
Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal drugs.

Vasospastic Angina (Prinzmetal's or Variant Angina)
Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy, or in combination with other antianginal drugs.

Angiographically Documented Coronary Artery Disease
In patients with recently documented coronary artery disease (CAD) by angiography and without heart failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure.

DOSAGE AND ADMINISTRATION:
For both hypertension and angina, the usual initial dose is 5 mg amlodipine once daily, which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

For patients with coronary artery disease, the recommended dosage range is 5 mg to 10 mg once daily. In clinical studies, the majority of patients required 10 mg once daily.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta-blockers, and ACE inhibitors.

Use in the Elderly
Normal dosage regimens are recommended. Amlodipine, used at similar doses in the elderly or younger patients, is equally well-tolerated.

Use in Children
Safety and effectiveness of amlodipine in children have not been established.

Use in Patients with Impaired Hepatic Function
See "Special warnings and precautions for use".

Use in Patients with Renal Failure
Amlodipine may be used at normal doses in patients with renal failure. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. Amlodipine is not dialyzable.

SIDE EFFECTS:
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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 not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders
Very rare: Allergic reactions

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Depression, mood changes (including anxiety), insomnia
Rare: Confusion

Nervous system disorders
Common: Somnolence, dizziness, headache (especially at the beginning of the treatment)
Uncommon: Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, extrapyramidal disorder
Very rare: Hypertonia, peripheral neuropathy

Eye disorders
Common: Visual disturbance (including diplopia)

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Common: Palpitations
Uncommon: Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Very rare: Myocardial infarction

Vascular disorders
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea
Uncommon: Cough, rhinitis

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

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

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Not known: Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Common: Ankle swelling, muscle cramps
Uncommon: Arthralgia, myalgia, back pain, muscle spasms

Renal and urinary disorders
Uncommon: Micturition disorder, nocturia, increased urinary frequency

Reproductive system and breast disorders
Uncommon: Impotence, gynaecomastia

General disorders and administration site conditions
Very common: Oedema
Common: Fatigue, asthenia
Uncommon: Chest pain, pain, malaise

Investigations
Uncommon: Weight increased, weight decreased

***mostly consistent with cholestasis**

DRUG INTERACTIONS:
Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin
Co-administration of multiple doses of 10 mg 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.

Grapefruit Juice
Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Co-administration of 240 mL grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, 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.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Co-administration of erythromycin in healthy volunteers (18 to 43 years of age) did not significantly change amlodipine systemic exposure (22% increase in area under the concentration versus time curve [AUC]). Although the clinical relevance of these findings is uncertain, pharmacokinetic variations may be more pronounced in the elderly.

Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution when administered with CYP3A4 inhibitors.

Clarithromycin
Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

CYP3A4 Inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g., rifampicin, *Hypericum perforatum* (St. John's Wort)) may decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

Special Studies: Effect of Other Agents on Amlodipine

Cimetidine

Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Aluminum/Magnesium (Antacid)

Co-administration of aluminum/magnesium (antacid) with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Amlodipine on Other Agents

Atorvastatin

Co-administration of multiple 10 mg doses of amlodipine with 80 mg atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin

Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (Alcohol)

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin

Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin

No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of amlodipine with cyclosporin affects the trough concentrations of cyclosporin, from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. 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.

Drug/Laboratory Test Interactions
None known

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Use in Patients with Heart Failure
In a long-term placebo-controlled study (PRAISE-2) of amlodipine in patients with New York Heart Association (NYHA), class III and IV heart failure of non-ischemic etiology, amlodipine was associated with increased reports of pulmonary edema despite no significant differences in the incidence of worsening heart failure compared to placebo.

Use in Patients with Impaired Hepatic Function
As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. The drug should therefore be administered with caution in these patients.

FERTILITY, PREGNANCY AND LACTATION
The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in animal reproductive studies other than delay in parturition and prolongation of labor in rats at a dose level 50 times the maximum recommended dose in humans. Accordingly, use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus. There was no effect on the fertility of rats treated with amlodipine (see "Preclinical safety data").

Experience in humans indicates that amlodipine is transferred into human breast milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy-induced hypertension was 0.85 following amlodipine administration at an initial dose of 5 mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6 mg and 98.7 mcg/kg, respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 mcg/kg.

PRECLINICAL SAFETY DATA
Carcinogenesis
Rats and mice treated with amlodipine in the diet for 2 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/m2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenesis
Mutagenicity studies revealed no drug-related effects at either the gene or chromosome levels.

Impairment of Fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg, on a mg/m2 basis).

*Based on patient weight of 50 kg.

OVERDOSE:
In humans experience with intentional overdose is limited.

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

Treatment
Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

CONTRAINDICATIONS:
Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines* or any of the inert ingredients.
* Amlodipine is a dihydropyridine calcium channel blocker.

STORAGE CONDITIONS:
Store below 30°C. Protect from light and moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

MANUFACTURED BY:
IND-SWIFT
Ind Swift Limited
Off. NH-21, Village Jawaharpur, Tehsil Derabassi,
District SAS Nagar (Mohali), Punjab - 140507, India.