PACKAGE INSERT TEMPLATE FOR AMLODIPINE TABLET

Brand or Product Name
[Product name] Tablet 5mg
[Product name] Tablet 10mg

Name and Strength of Active Substance(s)
Amlodipine besilate ….mg equivalent to amlodipine 5mg.
Amlodipine besilate ….mg equivalent to amlodipine 10mg.

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '10' on one side]

Pharmacodynamics
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.

Pharmacokinetics
Absorption
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 1/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. Absorption of amlodipine is unaffected by consumption of food.

Biotransformation/Elimination
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in the Elderly
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.

Indication
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.

Amlodipine is indicated for the first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine may be used alone, as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta-blockers.

Recommended Dosage
For both hypertension and angina the usual initial dose is 5mg amlodipine once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response. No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors.

Use in the Elderly
Normal dosage regimens are recommended. Amlodipine, used at similar doses in 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 section Warnings and Precautions

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.

Mode of Administration
Oral

Contraindications
Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines and amlodipine.

Warnings and Precautions
Use in Patients with Heart Failure
Amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure compared to placebo.

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

Effects on Ability to Drive and Use Machines
Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive or use machinery.

Interactions with Other Medicaments
Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. Amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

Effect of other agents on amlodipine

GRAPEFRUIT JUICE: 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.

SIMVASTATIN: Co-administration of amlodipine with 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.

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

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

SILDENAFIL: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

CYP3A4 INHIBITORS: It cannot be ruled out that 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 together with CYP3A4 inhibitors; however no adverse events attributable to such interaction have been reported.

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

Special Studies: Effect of amlodipine on other agents.

ATORVASTATIN: Co-administration of amlodipine with 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.

ETHANOL (alcohol): 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: Amlodipine co-administration with cyclosporin affect 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.

Statement on Usage During Pregnancy and Lactation

Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level fifty 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.

Adverse Effects / Undesirable Effects

Amlodipine is well tolerated. The most commonly observed side effects were :

System Organ Class	Undesirable Effects
Nervous System Disorders	Headache, dizziness, somnolence
Cardiac Disorders	Palpitations
Vascular Disorders	Flushing
Gastrointestinal Disorders	Abdominal pain, nausea
General Disorders and Administration Site Conditions	Edema, fatigue

Less commonly observed side effects in marketing experience include :

System Organ Class	Undesirable Effects
Blood and Lymphatic System Disorders	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	Hyperglycemia
Psychiatric Disorders	Insomnia, mood changes
Nervous System Disorders	Hypertonia, hypoesthesia/ paraesthesia peripheral neuropathy, syncope, taste perversion, tremor, extrapyramidal disorder
Eye Disorders	Visual disturbances
Ear and Labyrinth Disorders	Tinnitus
Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, rhinitis
Gastrointestinal Disorders	Altered bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Disorders	Alopecia, increased sweating, purpura, skin discoloration, urticaria

Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle cramps, myalgia
Renal and Urinary Disorders	Increased urinary frequency, micturition disorder, nocturia
Reproductive System and Breast Disorders	Gynecomastia, impotence
General Disorders and Administration Site	Asthenia, malaise, pain
Investigations	Weight increased/decreased

Rarely, allergic reaction including pruritus, rash, angioedema, and erythema multiforme. Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis).

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Overdose and Treatment
Overdose of amlodipine 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.

Administration of activated charcoal immediately after or up to two hours of amlodipine 10 mg ingestion has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases.

Clinically significant hypotension due to amlodipine overdose 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. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]