Pharmaniaga Amnoz Tablet 5 mg
Pharmaniaga Amnoz Tablet 10 mg

COMPOSITION

Amnoz Tablet 5mg
Each tablet contains Amlodipine Besylate 6.935mg equivalent to Amlodipine 5mg.
Amnoz Tablet 10mg
Each tablet contains Amlodipine Besylate 13.87mg equivalent to Amlodipine 10mg.

DESCRIPTION
Amnoz Tablet 5mg
White to off-white, emerald shaped tablets engraved 5 and score-line on one side and Pharmaniaga logo on the other side.
Amnoz Tablet 10mg
White to off-white, emerald shaped tablets engraved 10 and score-line on one side and Pharmaniaga logo on the other 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 requirement.

2) The mechanism of action of amlodipine also probably involves dilation 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 L/kg. Amlodipine bound to plasma protein approximately 97.5%. Absorption of amlodipine is unaffected by consumption of food.

Biotransformation/Elimination
The terminal plasma elimination half-life is about 30-50 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 patients. 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
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 (other than amlodipine) 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.

Chronic Stable Angina
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. Take Amnoz Tablet either with or without food. Swallow Amnoz Tablet whole with a drink of water.

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.

ROUTE OF ADMINISTRATION
Oral.

CONTRAINDICATIONS
Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines, amlodipine or any of the excipients.

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. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

Amlodipine should therefore be initiate 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.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

Effects on Ability to Drive and Use Machines
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

INTERACTIONS WITH OTHER MEDICAMENTS
Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, 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).

Effects 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: 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 regulations considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Special Studies: Effect of amlodipine on other agents
ATORVASTATIN: Co-administration of 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 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.

PREGNANCY
Safety of amlodipine in human pregnancy has not been established.
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.

LACTATION
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.

ADVERSE 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, increasing sweating, purpura, skin discoloration, urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle cramps, myalgia
Renal and Urinary Disorders	Increased urinary frequency, micturition disorders, nocturia
Reproductive System and Breast Disorders	Gynecomastia, impotence
General Disorders and Administration Site	Asthenia, malaise, pain
Investigations	Weight increased/decreased

Rarely, allergic rection including pruritus, rash, angioedema, and erythema multiforme. Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

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 hypertension 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 not 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 CONDITION
Store below 30°C.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORMS AND PACKAGING AVAILABLE
In box of 100 tablets (10 Alu-Alu blisters x 10 tablets)

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
No. 11A, Jalan P/1, Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

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