



AMLODIPINE (Tablets)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMLODIPINE 5mg and 10mg Tablet

2. QUALITY AND QUANTITATIVE COMPOSITION

Qualitative Composition:

Each film coated tablet contains:

Amlodipine besylate..... 5 mg of amlodipine

Amlodipine besylate..... 10mg of amlodipine

Excipients.....Q.S.

Colour: White or almost white or yellowish white

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	BP
2	Calcium hydrogen phosphate	BP
3	Anhydrous	BP
4	Sodium starch glycolate (type A)	BP
5	Magnesium Stearate	BP

Quantitative Composition:

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3. PHARMACEUTICAL FORM

Solid Dosage form (Tablets)

For 10mg - White or almost white or yellowish white round flat bevelled edged tablets with stylish 'A' on one side and 10 engraved on the other side.

For 5mg - White or almost white or yellowish white round flat bevelled edged tablets with stylish 'A' on one side and 5 engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amlodipine is indicated for the first line treatment of hypertension and can be used as a sole agent to control blood pressure in the majority of patient. 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 inhibitor.

Amlodipine is indicated for the first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) 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



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confirmed, Amlodipine maybe 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.

4.2 Posology and method of administration

Posology

Adults

AMLODIPINE, 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 diuretic, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment; therefore, the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population

Children and adolescents with hypertension from 6 years to 17 years of age.

The recommended antihypertensive oral dose in paediatric patient's ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Amlodipine 2.5 mg is not currently available and the 2.5 mg dose cannot be obtained with Amlodipine 5 mg tablets as these tablets are not manufactured to break into two equal halves. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).

Children under 6 years old

No data are available.

Method of administration

Tablet for oral administration.

4.3 Contraindications

Amlodipine is contraindicated in patients with:

- hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients listed in section 6.1.
- severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high-grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Cardiac failure:

Patients with heart failure should be treated with caution. In a long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). 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.

Hepatic impairment:

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Renal impairment:



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Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors:

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers:

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion):

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products:

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus:

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors:



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

Cyclosporine:

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin:

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, or warfarin.

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta-blockers, angiotensin-converting enzyme inhibitors, long acting nitrates, sublingual nitro glycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypo glycemia drugs. Special studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine. 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). In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

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

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7%, with a maximum of 15%. The effect of amlodipine

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

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ 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.

System Organ Class	Frequency	Adverse reactions
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	Insomnia, mood changes (including anxiety), depression

	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very Rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
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
Hepato-biliary disorders	Very Rare	Hepatitis, jaundice, hepatic enzymes 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
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynecomastia
General disorders and administration site conditions	Common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions is essential for continuous monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the Swipha Pharmacovigilance online ADR form www.swiphanigeria.com/adr_form . See Section 7 for more info.

4.9 Overdose

In humans experience with intentional overdose is limited

Symptoms:



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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.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment:

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: C08CA01

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

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

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

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

5.2 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

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly population



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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.

Paediatric population

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

5.3 Preclinical safety data

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg



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6.0 Pharmaceutical Particulars

6.1 List of excipients

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	BP
2	Calcium hydrogen phosphate	BP
3	Anhydrous	BP
4	Sodium starch glycolate (type A)	BP
5	Magnesium Stearate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C, protect from light.

Keep medicines out of reach of children.

Store in the original package.

6.5 Nature and contents of container

ALU- PVC/PVDC blister packs of 3X10's and 10 X 10 tablets.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER/ REGISTRANT

Swiss Pharma Nigeria Limited



AMLODIPINE (Tablets)

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8. MANUFACTURER DETAILS

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9. MARKETING AUTHORIZATION NUMBERS

A4-2280, A4-2279

10. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

11. DATE OF REVISION OF THE TEXT
