

SUMMARY OF PRODUCT CHARACTERISTICS

KARDAM

Amlodipine Besilate Tablets 5 mg and 10 mg

R_x only

1. **NAME OF DRUG PRODUCT** : Amlodipine Besilate Tablets 5 mg.
Amlodipine Besilate Tablets 10 mg.

(TRADE) NAME OF PRODUCT : KARDAM 5
KARDAM 10

STRENGTH : 5 mg and 10 mg,

PHARMACEUTICAL DOSAGE FORM: Tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Amlodipine Besilate Tablets 5 mg

Each uncoated tablet contains Amlodipine Besilate Ph.Eur. equivalent to Amlodipine 5 mg.

Amlodipine Besilate Tablets 10 mg

Each uncoated tablet contains Amlodipine Besilate Ph.Eur. equivalent to Amlodipine 10 mg.

3. PHARMACEUTICAL FORM:

Amlodipine Besilate Tablets 5 mg: White to off white, flat, bevel edged, barrel shaped, uncoated tablets debossed with 'C' on one side and '58' on the other side.

Amlodipine Besilate Tablets 10 mg: White to off white, flat, bevel edged, round uncoated tablets debossed with 'C' on one side and '59' on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Hypertension

Chronic stable angina pectoris

Vasospastic (Prinzmetal's) angina

4.2 Posology and method of administration

Posology

Adults

For both hypertension and angina the usual initial dose is 5 mg Amlodipine besilate once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

In hypertensive patients, Amlodipine besilate has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine besilate may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of Amlodipine besilate is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin converting enzyme inhibitors.

Special populations

Elderly patients

Amlodipine besilate 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.

Patients with 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. 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.

Patients with 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 patients 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. Doses in excess of 5 mg daily have not been studied in paediatric patients.

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. 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 has not been established.

Patients with 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. 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.

Patients with 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 patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

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 dialysable.

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 coadministration 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

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.

4.6 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.

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.

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.

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 ($< 1/10,000$).

Blood and the Lymphatic System Disorders

Very Rare: Leukocytopenia, Thrombocytopenia

Immune System Disorders

Very Rare: Allergic reaction. 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.

Uncommon: Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia.

Very Rare: Hypertonia, peripheral neuropathy.

Eye Disorders

Common: visual disturbances.

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 and 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

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

“Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: <https://imis.tmda.go.tz/arrt> or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store”;

4.9 Overdosage

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

Amlodipine besilate 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 besilate is due to a direct relaxant effect on vascular smooth muscle. Amlodipine besilate reduces total ischaemic burden by the following two actions.

- 1) Amlodipine besilate dilates peripheral arterioles and thus, reduces the total peripheral resistance (after load) 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 besilate 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 besilate administration.

In patients with angina, once daily administration of Amlodipine besilate 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 besilate is not 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 is estimated to be between 64 and 80%. The volume of distribution is approximately 21L/kg.

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 metabolized 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

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 besilate 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose, Sodium Starch Glycolate, Anhydrous Calcium Hydrogen Phosphate and Magnesium Stearate.

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

KARDAM 5 (Amlodipine Besilate Tablets 5 mg) -3 x 10's Tablets

KARDAM 10 (Amlodipine Besilate Tablets 10 mg) -3 x 10's Tablets

The container is a blister. Blister pack comprises of comprises of 250 µ white opaque PVC film coated with 90 gsm PVdC as a forming material and plain 25µ aluminium foil with 7 gsm heat seal lacquer as the lidding foil.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorization Holder

Aurobindo Pharma Limited.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038,
Telangana, State, India.

8. Marketing authorization number(s)

TAN 21 HM 0416

9. Date of first authorisation/renewal of the authorisation

2021-10-09

10. Date of revision of the text