SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMLOVAS 5 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Amlodipine besylate 6,944 mg (Equivalent to 5 mg amlodipine base)

Excipients:

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet

White, round, scored (It allows dividing the tablet to provide the 2.5 mg amlodipine dose in the pediatric population posology) tablets

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

1. Essential Hypertension:

It can be used alone or in combination with other antihypertensives to control blood pressure.

2. Coronary Artery Disease:

Chronic stable angina:

It is indicated for the symptomatic treatment of chronic stable angina. It can be used alone or in combination with other antianginal drugs.

Vasospastic or Prinzmetal's Angina:

It is indicated in the treatment of angina attacks due to vasospasm in the coronary vessels. It can be used alone or in combination with other antianginal drugs.

4.2. Posology and method of administration

Posology/administration frequency and duration:

The usual starting dose for hypertension and angina is 5 mg AMLOVAS once daily and depending on the individual patient's response, the dose may be increased to a maximum of 10 mg.

AMLOVAS in hypertensive patients; It has been used in combination with thiazide diuretics, alpha-blockers, beta-blockers or an angiotensin converting enzyme inhibitor. AMLOVAS can be used as monotherapy or in combination with other antianginal drugs in patients with angina who do not respond to nitrates and/or other appropriate doses of beta-blockers.

No dose adjustment of AMLOVAS is required when thiazide diuretics, beta-blockers, and angiotensin converting enzyme inhibitors are used with AMLOVAS.

Method of Application:

It is for oral use.

Additional information on special populations:

Liver failure:

Dosage recommendations have not been established for patients with mild to moderate hepatic impairment; therefore, dose selection should be made with care and should begin with the lowest dose of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine in severe hepatic impairment have not been studied. Amlodipine use should be started with the lowest dose and the dose should be increased gradually in patients with severe hepatic impairment.

Kidney failure:

AMLOVAS can be used in these patients at normal doses. Amlodipine plasma concentration changes are not related to the degree of renal impairment. Amlodipine is not dialyzable.

Pediatric population:

The recommended oral antihypertensive dose in pediatric hypertensive patients 6-17 years of age is 2.5-5 mg once daily as an initial dose. If target blood pressure is not achieved after four weeks, the dose may be increased to 5 mg per day. Doses greater than 5 mg per day have not been studied in pediatric patients (see sections 5.1 and 5.2). Because the tablets are scored, it is possible to administer 2.5 mg of amlodipine with this medicine.

The effect of amlodipine on blood pressure in patients under 6 years of age is unknown.

Geriatric population:

AMLOVAS was equally well tolerated when used at similar doses in elderly or young hypertensive patients. Therefore, normal dosing is recommended in the elderly; however, dose escalation should be done with caution (see sections 4.4 and 5.2).

4.3. Contraindications

AMLOVAS is contraindicated in those with the following diseases:

- Sensitivity to dihydropyridines (amlodipine is a dihydropyridine calcium channel blocker), amlodipine and any substance in the composition of the drug
- severe hypotension
- Shock (including cardiogenic shock)
- Left ventricular outflow obstruction (eg, high-grade aortic stenosis)
- Hemodynamically unstable heart failure after myocardial infarction

4.4. Special warnings and precautions for use

General

The vasodilatory effect of AMLOVAS begins gradually. Therefore, rare cases of acute hypotension have been reported after oral administration of AMLOVAS. AMLOVAS, like other peripheral vasodilators, should be used with caution, especially in patients with severe aortic stenosis.

Use in patients with heart failure:

Caution should be exercised when treating patients with heart failure. In a placebo-controlled, long-term study in patients with severe heart failure (New York Heart Society - NYHA III and IV), the reported incidence of pulmonary edema was higher in the amlodipine-treated group than in the amlodipine-treated group. (see section 5.1 Pharmacodynamic properties)

calcium channel blockers, including amlodipine; It should be used with caution in patients with congestive heart failure, as it may lead to an increased risk of future cardiovascular events and mortality.

Use in patients with hepatic dysfunction:
As with all other calcium channel antagonists, the half-life of AMLOVAS is prolonged in patients with impaired hepatic function and dosage recommendations have not been established in these patients. AMLOVAS should be administered with caution in these patients.

Use in elderly patients:
Dose escalation should be done with caution in elderly patients (see sections 4.2 and 5.2).

Use in kidney failure:
In these patients, amlodipine can be used at normal doses. Changes in amlodipine plasma concentrations do not correlate with the degree of renal impairment.
Amlodipine is not dialyzable.

4.5. Interactions with other medicinal products and other forms of interaction
Effect of other agents on amlodipine

CYP3A4 inhibitors: Concomitant use with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides such as erythromycin or clarithromycin, verapamil or diltiazem) may significantly increase plasma concentrations of amlodipine, increasing the risk of hypotension. The clinical significance of these pharmacokinetic changes may be more pronounced in the elderly. Therefore, clinical monitoring and dose adjustment may be required.

Inducers of CYP3A4: The plasma concentration of amlodipine may be altered if known inducers of CYP3A4 are co-administered. Therefore, blood pressure monitoring and dose adjustment should be considered during and after drug use, especially with potent CYP3A4 inducers (eg, rifampicin, aaron's beard).

Grapefruit juice: The use of amlodipine with grapefruit or grapefruit juice is not recommended as it may cause increased bioavailability in some patients, which may result in an increased blood pressure lowering effect.

Dantrolene (infusion): In animals, fatal ventricular fibrillation and cardiovascular collapse with hyperkalemia have been observed after administration of verapamil and intravenous dantrolene. Due to the risk of hyperkalemia, it is recommended to avoid co-administration of calcium channel blockers such as amlodipine in patients with suspected malignant hyperthermia and in the treatment of malignant hyperthermia.

Effect of amlodipine on other agents

The blood pressure lowering effect of amlodipine adds to the blood pressure lowering effect of other drugs with antihypertensive properties.

Tacrolimus:

Although the pharmacokinetic mechanics are not fully known, there is a risk of increased blood levels of tacrolimus when tacrolimus and amlodipine are used concomitantly. To avoid tacrolimus toxicity, when using amlodipine in patients treated with tacrolimus, the blood level of tacrolimus should be monitored and dose adjustments made if necessary.

Mechanical 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 the exposure of mTOR inhibitors.

Cyclosporine: No drug interaction studies have been conducted between cyclosporine and amlodipine in healthy volunteers or any other population, with the exception of renal transplant patients in whom unstable increases in cyclosporine concentration (mean 0% to 40%) were observed. Care should be taken to monitor cyclosporine levels in renal transplant patients receiving amlodipine, and the dose of cyclosporine should be reduced if necessary.

Simvastatin: Co-administration of repeated doses of 10 mg of amlodipine with 80 mg of simvastatin; caused a 77% increase in simvastatin exposure compared to simvastatin administration alone. The dose of simvastatin should be limited to 20 mg daily in patients receiving amlodipine therapy.

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

Additional information on special populations

Liver/kidney failure:

No interaction studies have been conducted.

Pediatric population:

No interaction studies have been conducted.

4.6. Pregnancy and lactation

General advice:

Pregnancy category is C.

Women of childbearing potential / Contraception

Women of childbearing potential should ensure that they use effective contraception.

Pregnancy period

The safety of AMLOVAS in humans during pregnancy has not been established. Accordingly, its use in pregnant women can only be recommended in cases where there is no safer treatment alternative and the disease itself carries a greater risk for the mother and fetus.

Animal studies are insufficient for effects on pregnancy/ and-or/ embryonal/ fetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3 Preclinical safety data). The potential risk for humans is unknown.

Lactation period

Amlodipine is excreted in human milk. The proportion of maternal dose ingested by the infant was estimated at quartiles of 3-7% and at most 15%. The effect of amlodipine on infants is unknown. Decision to continue/discontinue breastfeeding or continue/discontinue treatment with amlodipine; It should be given considering the benefit of breastfeeding for the child and the benefit of amlodipine therapy for the mother.

Reproductive ability / Fertility

Reversible biochemical changes in the sperm cell head have been reported in some patients treated with calcium channel blockers. Clinical data on the potential effect of amlodipine on

fertility are insufficient. Adverse effects on male fertility were found in a rat study (see section 5.3 Preclinical safety data).

4.7. Effects on the ability to drive and use machines

Amlodipine may have minor or moderate influence on the ability to drive and use machines. If patients receiving amlodipine experience drowsiness, headache, tiredness or nausea, their ability to react may be impaired. Caution is recommended, especially at the beginning of treatment.

4.8. Undesirable effects

Summary of the safety profile

The most common adverse reactions observed during treatment were somnolence, drowsiness, headache, palpitations, facial flushing, abdominal pain, nausea, ankle edema (swelling) and fatigue.

List of side effects in tabular form:

The following adverse events were observed 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) and unknown (cannot be estimated from the available data) are listed below:

Adverse reactions are listed in each frequency group in order of decreasing severity.

Blood and lymphatic system diseases

Very rare: Thrombocytopenia, leukopenia

Immune system diseases

Very rare: Allergic reaction

Metabolism and nutrition diseases

Very rare: Hyperglycemia

Psychiatric diseases

Uncommon:	Depression, mood swings (including anxiety), insomnia
Rare:	Confusion

Nervous system diseases

Common:	somnolence, drowsiness, headache (especially at the beginning of treatment)
Uncommon:	Tremor, taste perversion, syncope, hypoesthesia, paresthesia
Very rare:	Hypertonia, peripheral neuropathy

Eye diseases

Common:	Visual impairment (including diplopia)

Ear and inner ear diseases

Uncommon:	Tinnitus

Cardiac diseases

Common:	Palpitation (palpitation)
Uncommon:	Arrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)
Very rare:	Myocardial infarction

Vascular diseases

Common:	Facial flushing
Uncommon:	Hypotension
Very rare:	Vasculitis

Respiratory, thoracic and mediastinal diseases

Common:	Dyspnea
Uncommon:	Cough, rhinitis

Gastrointestinal diseases

Common: Abdominal pain, nausea, dyspepsia, change in bowel movements (including diarrhea and constipation)

Uncommon: Vomiting, dry mouth

Very rare: Pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary diseases

Very rare: Hepatitis, jaundice and liver enzyme elevations (mostly compatible with cholestasis)

Skin and subcutaneous tissue diseases

Uncommon: Alopecia, purpura, skin discoloration, increased sweating, pruritus, rash, exanthema, urticaria

Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke edema, photosensitivity

Unknown: Toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone diseases

Common : Ankle swelling, muscle cramps

Uncommon: Arthralgia, myalgia, back pain

Kidney and urinary tract diseases

Uncommon: micturition disorder, nocturia, increased frequency of urination

Reproductive system and breast diseases

Uncommon: Impotence, gynecomastia

General diseases and diseases related to the application site

Very common: Edema

Common: Fatigue, asthenia

Uncommon: Chest pain, pain, malaise

Studies

Uncommon: Weight gain/decrease

Exceptional cases of extrapyramidal syndrome have been observed.

4.9. Overdose and its treatment

Experience with deliberate overdose in humans is limited.

Symptoms

Available data suggest that large overdoses can lead to excessive peripheral vasodilation and possible reflex tachycardia. A few cases have also been reported, beginning with marked and possibly prolonged systemic hypotension and progressing to shock that resulted in death.

Treatment

Clinically significant hypotension due to amlodipine overdose requires active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of the extremities, and control of circulating fluid volume and volume of urine excreted.

A vasoconstrictor may be useful to restore vascular tone and blood pressure, provided there are no contraindications to its use. Intravenous calcium gluconate may be useful in counteracting the effects of calcium channel blocking.

In some cases, gastric lavage may be helpful. To healthy volunteers, amlodipine 10 mg orally When activated charcoal is given immediately after or up to 2 hours after ingestion, amlodipine.There was a significant decrease in absorption.

Dialysis would probably not be beneficial as amlodipine is highly protein bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiovascular system, selective calcium channel blocker 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 entry of calcium ions through the cell membrane into the cell in cardiac and vascular smooth muscles.
The antihypertensive mechanism of action of amlodipine is due to its direct relaxant effect on vascular smooth muscles. The exact mechanism of the relieving angina pectoris effect of amlodipine has not been fully determined, but amlodipine reduces the total ischemic load through the following two effects:

1. Amlodipine dilates peripheral arterioles, reducing the total peripheral resistance (afterload) that the heart faces. As the heart rate remains stable, unloading the heart reduces myocardial energy consumption and oxygen demand.
2. The mechanism of action of amlodipine is probably also related to dilation of the main coronary arteries and coronary arterioles in both normal and ischemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal or variant angina).

In patients with hypertension, once daily dosing produces clinically significant reductions in both supine and standing blood pressure over a 24-hour period. Acute hypotension is not observed with the use of amlodipine due to its slow onset of action.

In patients with angina, once-daily administration of amlodipine prolongs total exercise time, time to angina onset, time to 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerin tablet consumption. Metabolic adverse effects or changes in plasma lipids have not occurred with amlodipine and are suitable for use in patients with asthma, diabetes, and gout.

The efficacy of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) was evaluated in an independent, multicenter, double-blind, placebo-controlled study of 1997 patients, Comparison of Amlodipine and Enalapril in Limiting Thrombosis Cases (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis, CAMELOT). Alongside standard of care with statins, beta-blockers, diuretics, and aspirin, 655 of these patients were treated with placebo, 673 with enalapril 10-20 mg, and 663 with amlodipine 5-10 mg for 2 years. The main efficacy results are shown in Table 1. The results showed that amlodipine treatment reduced hospitalization and revascularization attempts due to angina in patients with CAD.

Table 1. Incidence of Significant Clinical Outcomes in CAMELOT					
	Cardiovascular event rateNo. (%)			**Amlodipine vs. placebo**	
Clinical Result	**Amlodipine**	**Placebo**	**Enalapril**	**Risk ratio (95% Confidence Interval -CI)**	***P* value**
Primary endpoint					
cardiovascular undesirable effects	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54 – 0.88)	.003
Individual components					
Coronary Revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54 – 0.98)	.03
Hospitalization for Angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41 – 0.82)	.002
Non-fatal myocardial infarction	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37 – 1.46)	.37
Stroke or transient ischemic attack	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19 – 1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48 – 12.7)	.27
Hospitalization for congestive heart failure	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14 – 2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50 – 13.4)	.24

Use in patients with heart failure

Hemodynamic and exercise-based controlled clinical studies in NYHA Class II - IV heart failure patients showed that amlodipine; showed no clinical deterioration as determined by exercise tolerance, left ventricular ejection fraction measurements, and clinical symptomatology.

In a placebo-controlled study (PRAISE) in patients with NYHA Class III - IV heart failure receiving digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitors, it was shown that amlodipine did not result in an increased risk of mortality or combined mortality and morbidity in patients with heart failure.

In a long-term, placebo-controlled follow-up study (PRAISE - 2) in patients with NYHA III and IV heart failure of non-ischemic etiology and using stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on total or cardiovascular mortality. In the same population, there was an increase in reports of pulmonary edema with the use of amlodipine, but there was no significant difference in the incidence of aggravation of heart failure compared to placebo.

Heart Attack Prevention Treatment Trial (ALLHAT)
Antihypertensive and lipid-lowering therapy study to Prevent Heart Attack (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ALLHAT), This is a randomized, double-blind morbidity-mortality study to compare the new drugs amlodipine (calcium channel blocker) (2.5-10 mg/day) and chlortalidone (12.5-25 mg/day), a thiazide diuretic with lisinopril (angiotensin converting enzyme (ACE) inhibitor) (10-40 mg/day), for the initial treatment of mild to moderate hypertension.

A total of 33 357 hypertensive patients aged 55 years or older were randomized and followed for a mean of 4.9 years. In addition, patients had at least one of the following risk factors; >6 months prior, myocardial infarction or stroke, or other documented cardiovascular disease (51.5% overall), type 2 diabetes (36.1%), HDL-C <35 mg/dL (11.6%), electrocardiogram or left ventricular hypertrophy (20.9%) diagnosed by echocardiography, smoking (21.9%).

The primary endpoint was a combination of fatal CAD and non-fatal myocardial infarction. In the primary endpoint, there was no significant difference between amlodipine-based therapy and chlorthalidone-based therapy (RR 0.98 95% CI [0.90-1.07] p=0.65). Among the

secondary endpoints, the incidence of heart failure (a composite combined cardiovascular endpoint component) was significantly higher in the amlodipine group than in the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). On the other hand, there was no significant difference in mortality from any cause between amlodipine-based treatment and chlorthalidone-based treatment (RR 0.96 95% CI [0.89-1.02] p=0.20).

Use in pediatric patients (6-17 years old)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, 2.5 mg and 5 mg doses of amlodipine were compared with placebo, both doses reducing systemic blood pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty, and general development have not been studied. The long-term effect of amlodipine treatment in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been demonstrated.

5.2 Pharmacokinetic properties

General features:

Absorbation:

After oral administration of therapeutic doses, amlodipine is well absorbed, producing peak blood levels 6 to 12 hours post-dose. Absolute bioavailability has been calculated between 64 – 80%.

Taking it with food does not affect the absorption of amlodipine.

Distribution:

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.

Biotransformation:

Steady state plasma levels are reached after 7 to 8 days with successive doses. Amlodipine is extensively metabolized in the liver to inactive metabolites, with 10% of the parent drug and 60% of its metabolites excreted in the urine.

Elimination:

The terminal plasma elimination half-life is approximately 35-50 hours and is consistent with the once-daily recommendation.

Linearity / Non-linear case

Data not available.

Characteristics in patients

Use in elderly patients:

The time to peak plasma concentrations of amlodipine is similar in the elderly and the young. Amlodipine clearance in the elderly; tends to decrease resulting in increased area under the curve (AUC) and elimination half-life. The increase in area under the curve (AUC) and elimination half-life in patients with congestive heart failure was as expected for the patient age group studied.

Use in patients with hepatic impairment:

Very limited clinical data are available on the use of amlodipine in patients with hepatic impairment. It has a longer half-life and low clearance of amlodipine resulting in an approximately 40-60% increase in AUC in patients with hepatic impairment.

Use in pediatric patients:

A population pharmacokinetic study was conducted in 74 hypertensive children aged 1 to 17 years (34 patients 6-12 years and 28 patients 13-17 years) receiving amlodipine 1.25 to 20 mg once or twice daily. Typical oral clearance (CL/F) in children aged 6-12 years and adolescents aged 13-17 years was 22.5 and 27.4 l/hr in males and 16.4 and 21.3 l/hr in females, respectively. High variability in interindividual exposure has been observed. Data reported in children under 6 years of age are limited.

5.3 Preclinical safety data

Reproductive toxicology

Reproductive studies in rats and mice showed delayed delivery, prolonged duration of labor and reduced pup survival at doses greater than approximately 50 times the maximum recommended human dose on a mg/kg basis.

Carcinogenesis

There was no evidence of carcinogenesis in mice and rats given amlodipine at concentrations equivalent to 0.5, 1.25, and 2.5 mg/kg/day for two years. The highest dose (in mg/m^2, similar to the maximum recommended human clinical dose of 10 mg for rats and twice the maximum recommended human clinical dose of 10 mg for rats*) is close to the maximum tolerated dose for mice; but not for rats.

Mutagenesis

Mutagenesis studies did not show any drug-related effects at the gene or chromosomal level.

Fertility Disorders

No effects on fertility were seen in rats (64 days pre-mating males 14 days females) at doses up to 10 mg/kg/day (eight times the maximum recommended human dose of 10 mg on a mg/m^2 basis*). In another rat study in male rats treated for 30 days with amlodipine at a dose comparable to the human dose on a mg/kg basis; decreases was observed in the amount of plasma follicle stimulating hormone and testosterone were observed, as were decreases in sperm density and the number of adult spermatids and Sertoli cells.

* Patient weight is assumed to be 50 kg.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Microcrystalline cellulose

Anhydrous dibasic calcium phosphate

Sodium starch glycolate

Magnesium stearate

6.2 Incompatibilities

Not available.

6.3 Shelf life

36 months.

6.4 Special warnings for storage

It should be stored at room temperature below 25°C.

6.5 The nature and content of the packaging

In box, PVC/PVDC/Aluminum blister.

Packs of 20, 30 and 90 tablets.

6.6 Disposal of residues from the medicinal product for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

194 / 10 (in Turkey)

9. FIRST REGISTRATION DATE/REGISTRATION RENEWAL DATE

First Registratıon Date: 28.10.1999 (in Turkey)

Registration Renewal Date: 04.06.2005 (in Turkey)

10. RENEWAL DATE OF SPC

23/05/2019