Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Amlovie 10

Amlodipine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg amlodipine (as amlodipine besilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to almost white, oblong tablet, scored on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Hypertension
- Chronic stable angina pectoris.
- Vasospastic (Prinzmetal's) angina pectoris.

4.2. Posology and mode of administration

4.2.1. Posology

Adults

For treatment of both hypertension and angina pectoris the usual initial dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks this dose may be increased to a maximum dose of 10 mg daily (as single dose) depending on the individual patient's response.

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-blocker, or an angiotensin converting enzyme inhibitor.

For angina, amlodipine 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 is required upon concomitant administration of thiazide diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors.

4.2.2. Special populations

- 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.

- 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.

- 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.

4.2.3. Pediatric population

- Children 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. Doses in excess of 5 mg daily have not been studied in paediatric patients.
  Administration of 2,5 mg dose is not possible with a tablet of Amlovie 10.

- Children under 6 years old: the effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

4.2.4. Method of administration

Tablet for oral administration.

4.3. Contraindications

Amlodipine is contra-indicated in patients with:

- hypersensitivity to amlodipine, dihydropyridine derivatives or 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 warning and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis has 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, but this was not indicating an aggravation of the heart failure. 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.
- Myocardial infarction.

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

  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.
- Renal failure

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

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4.5. Interactions with other medicinal products and other forms of interactions

<u>Effects of other medicinal products on amlodipine</u>

- **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.
  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).
- Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, 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.
- Consumption of grapefruit/grapefruit juice should be avoided while taking amlodipine. The intake of grapefruit juice may result in increased plasma amlodipine concentrations, which may enhance the blood pressure lowering effects of amlodipine. This interaction has been observed with other dihydropyridine calcium antagonists and represents a class effect.

<u>Effects of amlodipine on other medicinal products</u>

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporine.
- Data from in vitro human plasma studies indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.
- The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.
- 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.
- Trimethoprim and in fixed dose combination with sulfamethoxazole (Co-trimoxazole): an increased incidence of hyperkalaemia was observed in patients

taking ACE Inhibitors and trimethoprim and in fixed dose combination with sulfamethoxazole (Co-trimoxazole).

- 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.
- 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.

4.6. Fertility, pregnancy and lactation

4.6.1. Pregnancy

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.

4.6.2. 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.

4.6.3. Fertility

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.

4.7. Effects on the 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 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 undesirable effects have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to ≤1/100), Rare (≥1/10 000 to ≤1/1000), Very rare (≤1/10 000), Not known (Frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Undesirable effects : event and frequency per organ system class	
Blood and lymphatic system disorders	
Leukocytopenia, thrombocytopenia	Very rare
Immune system disorders	
Allergic reactions	Very rare
Endocrine disorders	
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Not known
Metabolism and nutrition disorders	
Hyperglycaemia	Very rare
Psychiatric disorders	
Insomnia, mood changes (including anxiety), depression	Uncommon
Confusion	Rare
Nervous system disorders	
Somnolence, dizziness, headache (especially at the beginning of the treatment)	Common

Undesirable effects : event and frequency per organ system class	
Tremor, dysgeusia, syncope, hypoesthesia, paresthesis	Uncommon
Hypertonia, peripheral neuropathy	Very rare
Extrapyramidal disorder	Not known
Eye disorders	
Visual disturbance (including diplopia)	Common
Ear and labyrinth disorders	
Tinnitus	Uncommon
Cardiac disorders	
Palpitations	Common
Arrhythmia (including bradycardia and atrial fibrillation)	Uncommon
Myocardial infarction	Very rare
Vascular disorders	
Flushing	Common
Hypotension	Uncommon
Vasculitis	Very rare
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	Common
Rhinitis, cough	Uncommon
Gastrointestinal disorders	
Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)	Common
Vomiting, dry mouth	Uncommon
Pancreatitis, gastritis, gingival hyperplasia	Very rare
Hepatobiliary disorders	
Hepatitis, jaundice, hepatic enzymes increased*	Very rare
Skin and subcutaneous tissue disorders	
Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria	Uncommon
Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity	Very rare

Undesirable effects : event and frequency per organ system class	
Toxic Epidermal Necrolysis	Not known
Musculoskeletal and connective tissue disorders	
Ankle swelling, muscle cramps	Common
Arthralgia, myalgia, back pain	Uncommon
Renal and urinary disorders	
Micturition disorder, nocturia, increased urinary frequency	Uncommon
Reproductive system and breast disorders	
Impotence, gynecomastia	Uncommon
General disorders and administration site conditions	
Oedema	Very common
Fatigue, asthenia	Common
Chest pain, pain, malaise	Uncommon
Investigations	
Weight increase, weight decrease	Uncommon

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

4.9. Overdose

In humans, experience with intentional overdose is limited.

- Symptoms

  Available data suggest that large 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.

- Management

  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 10mg 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 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:

- 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.
- 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 dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

<u>Clinical efficacy and safety</u>
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.

- In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both supine and standing positions throughout

the 24 hour interval. Due to 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, the delay of occurrence of anginal attack and the delay of the occurrence of a 1-mm ST interval. Amlodipine decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

- Coronary artery disease (CAD)
  The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in the following table. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Incidence of significant clinical outcomes for CAMELOT

	cardiovascular event rates, Number. (%)			amlodipine versus placebo	
Evaluation criteria	amlodipine	placebo	enalapril	hazard ratio (95% CI)	p value
Primary endpoint					
Adverse cardiovascular events	110 (16,6)	151 (23,1)	136 (20,2)	0,69 (0,54-0,88)	0,003
Individual components					
Coronary revascularization	78 (11,8)	103 (15,7)	95 (14,1)	0,73 (0,54-0,98)	0,03
Hospitalization for angina	51 (7,7)	84 (12,8)	86 (12,8)	0,58 (0,41-0,82)	0,002
Nonfatal MI	14 (2,1)	19 (2,9)	11 (1,6)	0,73 (0,37-1,46)	0,37
Stroke or TIA	6 (0,9)	12 (1,8)	8 (1,2)	0,50 (0,19-1,32)	0,15
Cardiovascular death	5 (0,8)	2 (0,3)	5 (0,7)	2,46 (0,48-12,7)	0,27
Hospitalization for CHF	3 (0,5)	5 (0,8)	4 (0,6)	0,59 (0,14-2,47)	0,46
Resuscitated cardiac arrest	0	4 (0,6)	1 (0,1)	NA	0,04
New-onset peripheral vascular disease	5 (0,8)	2 (0,3)	8 (1,2)	2,6 (0,50-13,4)	0,24

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack

- Use in patients with heart failure
  Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.
  A placebo-controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.
  In a follow-up, long term, placebo-controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

- Treatment to prevent heart attack trial (ALLHAT):
  A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.
  A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
  The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure

(component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% % vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

- Use in children (aged 6 years and older):
  In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of amlodipine with placebo, showed that both doses reduced Systolic 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 efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2. Pharmacokinetic properties

- Absorption, distribution, binding to plasmatic proteins
  After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose.
  Absolute bioavailability of the unchanged active substance is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours after administration.
  The volume of distribution is approximately 21 l/kg. The pKa of amlodipine is 8.6. In vitro studies have shown that amlodipine is bound to plasmatic proteins up to 97.5%.
  Absorption of amlodipine is not influenced by concomitant food intake.

- Biotransformation and elimination
  Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound.
  The plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. 60% of metabolites are 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 patients
  The time to reach peak plasma concentrations is similar in elderly and younger patients. The clearance tends to be decreased with resulting increases in AUC and terminal elimination half-life in elderly patients. Increase 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 21.3L/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, this is 8 times (based on patient weight of 50kg) 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 and 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 (based on patient weight of 50kg) 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Microcrystalline cellulose
- Calcium hydrogen phosphate dihydrate
- Sodium starch glycolate (Type A)
- Magnesium stearate

6.2. Incompatibilities

None stated.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30° C.

6.5. Nature and contents of container

Opaque PVC-PVDC/Aluminium blister.

Box containing 30 tablets (3 blisters of 10 tablets).

6.6. Special precautions for disposal and other handlings

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Bluepharma Indústria Farmacêutica S.A., S. Martinho do Bispo,3045-016 Coimbra, Portugal.

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

January 2019.