

**1.3 Product Information**

**1.3.1 Summary of Product Characteristics (SmPC)**

*====Attached====*

**Summary of Product Characteristics**  
**Dilopax (Amlodipine Besylate Tablets USP 5 mg /10 mg)**

**1. Name of the medicinal product**

Amlodipine Besylate Tablets USP 5 mg /10 mg

**2. Qualitative and quantitative composition**

Each uncoated tablet contains:

Amlodipine Besylate USP

equivalent to Amlodipine 5 mg /10 mg

**3. Pharmaceutical form**

Uncoated Tablet.

White coloured, round shaped, biconvex uncoated tablets.

**4. Clinical particulars**

**4.1 Therapeutic indications**

Hypertension

DILOPAX is indicated for the treatment of hypertension. It may be used alone or in combination with other anti hypertensive agents.

Coronary Artery Disease (CAD)

Chronic Stable Angina

DILOPAX is indicated for the symptomatic treatment of chronic stable angina. DILOPAX may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

DILOPAX is indicated for the treatment of confirmed or suspected vasospastic angina. DILOPAX may be used as monotherapy or in combination with other antianginal drugs.

**4.2 Posology and method of administration**

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. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

In children (less than 18 years of age)

Use of amlodipine in children is not recommended.

In the elderly

Normal dosage regimens are recommended in the elderly, but caution should be exercised when increasing the dosage.

In patients with renal impairment

In these patients amlodipine can be used in the normal dosage. Amlodipine is not dialyzable.

In patients with hepatic impairment

A dosage regimen for patients with hepatic impairment has not been established; therefore amlodipine should be administered with caution. The tablets should be taken with a glass of water independently from meals.

In pregnancy and breastfeeding Animal studies have failed to reveal evidence of teratogenicity or foetal toxicity. There are no controlled data in human pregnancy. Amlodipine should be avoided during pregnancy but the risk to the foetus should be balanced against the risk of uncontrolled maternal hypertension.

The use of Amlodipine is not recommended during breastfeeding. Some mothers appear to excrete amount of Amlodipine in milk that might affect some breastfed infants. Until more safety data become available, an alternate drug may be preferred

### **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**

Increased Angina and/or Myocardial Infarction

**Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute**

Interaction with other medicinal products and other forms of interaction myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Amlodipine should be administered with caution to patients with low cardiac reserve.

Patients with heart failure

Patients with cardiac failure should be treated with caution. In a long-term study including patients suffering from severe heart failure (NYHA grade 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.

Use in patients with impaired hepatic function.

The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution, in these patients.

Use in elderly patients

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

Use in children

Amlodipine should not be given to children due to insufficient clinical experience.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Use of pregnancy & breastfeeding** The safety of Amlodipine in human pregnancy has not been established. Amlodipine should only be given during pregnancy when the benefit outweighs the risk. The use of Amlodipine is not recommended during breastfeeding. Some mothers appear to excrete amounts of Amlodipine in milk that might affect some safety data become available, an alternate drug may be preferred.

#### **4.5 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).

#### **4.6 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.

#### 4.7 Undesirable effects

If you experience any of the following serious side effects, stop taking amlodipine and contact your doctor immediately or seek emergency medical treatment:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
- unusually fast or slow heartbeat;
- chest pain;
- severe dizziness or fainting;
- psychosis;
- jaundice (yellowing of the skin or eyes); or
- Swelling of the legs or ankles.

#### Drug Interactions

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: A study of elderly patients has shown that diltiazem inhibits metabolism of amlodipine, probably via CYP3A4, since plasma concentration increases by approximately 50% and the effect of amlodipine is increased. It cannot be excluded that stronger inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) increase the plasma- concentration of amlodipine to a greater extent than diltiazem. Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors.

CYP3A4 inducers: There is no information available on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's wort) on amlodipine. Co administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

In clinical interaction studies grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products

Amlodipine may potentiate the effect of other antihypertensives such as beta-adrenoceptor blocking agents, ACE-inhibitors, alpha-1- blockers and diuretics. In patients with an increased risk (for example after myocardial infarction) the combination of a calcium channel blocker with a beta-adrenoceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

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

There is no effect of amlodipine on laboratory testing.

#### 4.8 Overdose

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 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.

### Use in patients with 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 Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

<b>Table 1. Incidence of significant clinical outcomes for CAMELOT</b>					
Outcomes	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
	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)	.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
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	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 CHF	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

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

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine Besylate Tablets USP 10 mg 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 Besylate Tablets USP 10 mg 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 Besylate Tablets USP 10 mg in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine Besylate Tablets USP 10 mg had no effect on total cardiovascular mortality. In this same population Amlodipine Besylate Tablets USP 10 mg was associated with increased reports of pulmonary oedema.

#### Treatment to prevent heart attack trial (ALLHAT)

A randomised double-blind morbidity-mortality study called the Antihypertensive and LipidLowering 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 randomised 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 enrollment) 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 2.5 mg dose, and 5.0 mg 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 has also not been established.

## **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*

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/m 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/m 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**

Corn Starch Povidone K-30

Dibasic calcium phosphate

Microcrystalline cellulose

Talc

Magnesium stearate

Colloidal silicon dioxide

Croscarmellose sodium

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package.

Keep out of the reach and sight of children.

### **6.5 Nature and contents of container**

Alu-Alu Blister pack of 3 x10 tablets packed in carton along with package insert.

### **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 authorisation holder**

Korlyns Pharmaceuticals Limited.

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Maryland, Lagos, Nigeria.

Telephone number: +2349064597759.

E-mail Address: korlyns@korlynspharm.com

**8. Marketing authorisation number(s)**

A4 - 2915

**9. Date of first authorisation/renewal of the authorization**

-26th August, 2020

**10. Date of revision of the text**

25.05.2020