# SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

## 1. NAME OF THE MEDICINAL PRODUCT

NORVAPREF (Amlodipine Besylate Tablets USP 10 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Composition:**

Each uncoated tablet contains:

Amlodipine Besylate USP Equivalent to Amlodipine 10 mg

Excipients: q.s.

**Batch Size:** 10,000 tablets

| S.N. | Ingredients | Spec. | Qty/ Tab (mg) | Std. batch qty (gm) |
|---|---|---|---|---|
| 1 | Amlodipine Besylate Equivalent to Amlodipine | USP | 13.88 | 138.80 |
| 2 | Micro crystalline cellulose | BP | 113.14 | 1131.40 |
| 3 | Dibasic calcium phosphate | BP | 56.58 | 565.80 |
| 4 | Sodium starch glycolate | BP | 3.80 | 38.00 |
| 5 | Magnesium stearate | BP | 7.60 | 76.00 |
| | **Total** | | **195.00** | |

USP: United States Pharmacopoeia

BP: British Pharmacopoeia

Average weight of uncoated tablet: 195.00 mg ± 7.5 %

## 3. PHARMACEUTICAL FORM

Uncoated tablet

## 4.CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

• Hypertension

• Prophylaxis of chronic stable angina pectoris.

• Prinzmetal's (variant) angina when diagnosed by a cardiologist

In hypertensive patients, amlodipine tablets have been used in combination with a thiazide diuretic, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, amlodipine tablets may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
Amplodipine tablets are well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

## 4.2. POSOLOGY AND METHOD OF ADMINISTRATION

***In adults:*** For both hypertension and angina the usual initial dose is 5 mg Amlodipine tablets once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response. No dose adjustment of amlodipine tablets is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

***Use in children:*** Children 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. The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.
The 2.5 mg dose cannot be obtained with Amlodipine tablets 5 mg as these tablets are not manufactured to break into two equal halves.

***Use in the elderly:*** Amlodipine tablets, used at similar doses in elderly or younger patients, is equally well tolerated. Hence normal dosage regimens are recommended but increase of dosage should take place with care.
***Patients with hepatic impairment:*** See Special warnings and precautions for use.
***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.

## 4.3 CONTRAINDICATIONS

Amlodipine tablets are contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.
Amlodipine tablets should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina), severe hypotension.

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

***Use in patients with Heart Failure***

In a long-term, placebo controlled study (PRAISE-2) of amlodipine tablets in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 "Pharmacodynamic Properties"

***Use in patients with impaired hepatic function***

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of Amlodipine tablets alone, during or within one month of a myocardial infarction.

The safety and efficacy of Amlodipine tablets in hypertensive crisis has not been established.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND PHARMACEUTICAL FORM

Amlodipine tablets have been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long- acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

*In vitro* data from studies with human plasma indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indometacin.

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: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Consumption of grapefruit/grapefruit juice should be avoided while taking Amlodipine tablets. 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.

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

***Special Studies: Effect of other agents on amlodipine***

***Cimetidine:*** Co-administration of Amlodipine tablets with cimetidine did not alter the pharmacokinetics of Amlodipine tablets.

***Sildenafil:*** When Amlodipine tablets and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

***Special Studies: Effect of amlodipine on other agents***

***Atorvastatin:*** Co-administration of multiple 10mg doses of Amlodipine tablets with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

***Digoxin:*** Co-administration of Amlodipine tablets with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

***Warfarin:*** In healthy male volunteers, the co-administration of Amlodipine tablets does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of Amlodipine with warfarin did not change the warfarin prothrombin response time.

***Ciclosporin:*** Pharmacokinetic studies with ciclosporin have demonstrated that Amlodipine tablets do not significantly alter the pharmacokinetics of ciclosporin.

***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 to 20 mg daily in patients on amlodipine.

***Drug/Laboratory test Interactions*****:** None known.

## 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**

It is not known whether amlodipine is excreted in breast milk. 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.

## 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

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

| | | |
|---|---|---|
| *Blood and the Lymphatic System Disorders* | Thrombocytopenia<br>leukocytopenia | Very Rare |
| *Immune System Disorders* | allergic reaction | Very Rare |
| *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 |
| | tremor, taste perversion, syncope, hypoaesthesia, paraesthesia | Uncommon |
| | Peripheral neuropathy, hypertonia | Very Rare |
| *Eye Disorders* | visual disturbances (including diplopia) | Uncommon |
| *Ear and Labyrinth Disorders* | tinnitus | Uncommon |
| *Cardiac Disorders* | palpitations | Common |
| | myocardial infarction, arrhythmia, (including | Very Rare |

| | | |
|---|---|---|
| | bradycardia,ventricular tachycardia and atrial fibrillation) | |
| *Vascular Disorders* | flushing | Common |
| | hypotension | Uncommon |
| | vasculitis | Very Rare |
| *Respiratory, Thoracic and Mediastinal Disorders* | dyspnoea, rhinitis | Uncommon |
| | coughing | Very Rare |
| *Gastrointestinal Disorders* | abdominal pain, nausea | Common |
| | vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth | Uncommon |
| | pancreatitis, gastritis, gingival hyperplasia | Very Rare |
| *Hepato-biliary Disorders* | hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) | Very Rare |
| *Skin and Subcutaneous Tissue Disorders* | alopecia, purpura, skin discolouration, increased sweating, pruritus, rash, exanthema hyperhidrosis | Uncommon |
| | angioedema, erythema multiforme, urticaria, exfoliative dermatitis, stevens-johnson syndrome, quincke oedema, photosensitivity | Very Rare |
| *Musculoskeletal and Connective Tissue Disorders* | arthralgia, myalgia, muscle cramps, back pain | Uncommon |
| | ankle swelling | Common |
| *Renal and Urinary Disorders* | micturition disorder, nocturia, increased urinary frequency | Uncommon |
| *Reproductive System and Breast Disorders* | impotence, gynaecomastia | Uncommon |
| *General Disorders and Administration Site Conditions* | oedema, fatigue | Common |
| | chest pain, asthenia, pain, malaise | Uncommon |
| *Investigations* | weight increase, weight decrease | Uncommon |

## 4.9 OVERDOSAGE

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.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. 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. Since Amlodipine tablets are highly protein-bound, dialysis is not likely to be of benefit.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMICS PROPERTIES

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

1) Amlodipine tablets dilate peripheral arterioles and thus, reduce 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 tablets 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 tablets administration.

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

Amlodipine tablets have 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 Heart Failure***

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II- IV heart failure patients have shown that amlodipine tablets did not lead to clinical deteriorations 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 tablets 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 tablets 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 tablets had no effect on total cardiovascular mortality. In this same population Amlodipine tablets were associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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 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.

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, 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. Invitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

**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.

**Use in the elderly:** 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.
A population PK study has been conducted in 74 hypertensive children aged from 12 months 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

Not applicable

## 6.PHARAMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

| S.N. | Excipients | Specification |
|---|---|---|
| 1 | Micro crystalline cellulose | As per BP |
| 2 | Dibasic calcium phosphate | As per BP |
| 3 | Sodium starch glycolate | As per BP |
| 4 | Magnesium stearate | As per BP |

BP: British Pharmacopoeia

## 6.2 INCOMPATIBILITY

None such data reported

## 6.3 SHELF LIFE

36 months

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C. Protect from direct sunlight, heat & moisture.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Blister pack of 14 tablets

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSABLE AND OTHER HANDLING

None such special precautions for disposing and handling applies for this product.