BAFNA PHARMACEUTICALS LTD.,
www.bafnapharma.com INDIA.

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

1. Name of the medicinal product:

S-Amlodipine Besilate Tablets 5 mg

2. Qualitative and quantitative composition

Each uncoated tablet contains:

S-Amlodipine Besilate is equivalent to S-Amlodipine 5 mg

UNIT FORMULA

Sr. No.	Ingredients	Specification	Qty / Tablet (mg)	% Overages	Reason for inclusion
Active					
1	S-Amlodipine Besilate*	MS	6.950	Nil	Active
Excipients					
2	Microcrystalline Cellulose (PH 102) **	BP	137.226	Nil	Lubricant
3	Sodium Starch Glycolate (Type-A)	BP	3.840	Nil	Disintegrant
4	Croscarmellose Sodium	BP	7.680	Nil	Disintegrant
5	Crospovidone (polyplasdone XL – 10)	BP	1.216	Nil	Binder
6	Sodium Acid Citrate	BP	0.128	Nil	Preservative
7	Colloidal Anhydrous Silica	BP	0.400	Nil	Glidant
8	Magnesium Stearate	BP	2.560	Nil	Lubricant

Note:

*** 6.950 mg of S-Amlodipine Besilate MS equivalent to S-Amlodipine 5 mg**

*Actual quantity of S-Amlodipine Besilate MS to be dispensed is based on actual % purity of S-Amlodipine Besilate MS from the Batch formula worksheet as per subsequent calculation.

** Quantity of Microcrystalline Cellulose BP (PH 102) should adjust to the target weight as per the calculation shown in the Batch formula Worksheet.

Target weight per uncoated tablet	**:**	**160.000mg**

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

3. Pharmaceutical form

Uncoated tablet.

White to off white colour, circular shape, biconvex, Uncoated tablets plain on both sides.

4. Clinical particular

4.1 Therapeutic indications:

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration

Usual Adult Amlodipine Dose for Hypertension:

Initial dose: 5 mg orally once a day

Maintenance dose: 5 to 10 mg orally once a day

Small or fragile patients may be started on 2.5 mg orally once a day.

Usual Adult Amlodipine Dose for Angina Pectoris:

Chronic stable or vasospastic angina, or angiographically documented coronary artery disease in patients without heart failure or an ejection fraction less than 40%: 5 to 10 mg orally once a day

Most patients with chronic stable or vasospastic angina require 10 mg for adequate effect. In clinical studies, most patients with coronary artery disease required 10 mg.

Usual Adult Amlodipine Dose for Coronary Artery Disease:

Chronic stable or vasospastic angina, or angiographically documented coronary artery disease in patients without heart failure or an ejection fraction less than 40%: 5 to 10 mg orally once a day

Most patients with chronic stable or vasospastic angina require 10 mg for adequate effect. In clinical studies, most patients with coronary artery disease required 10 mg.

Usual Geriatric Amlodipine Dose for Hypertension:

Initial dose: 2.5 mg orally once a day

Maintenance dose: 2.5 to 10 mg orally once a day

Usual Geriatric Dose for Angina Pectoris:

Chronic stable or vasospastic angina: 5 to 10 mg orally once a day

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

The lower dose is recommended in the elderly; however, most patients require 10 mg for adequate effect.

Usual Pediatric Dose for Hypertension:

6 to 17 years: 2.5 mg to 5 mg orally once a day

Doses in excess of 5 mg daily have not been studied in pediatric patients.

Method of administration

For oral administration only.

4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

4.4 Special warnings and precautions for use

Use in patients with heart failure

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic 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.

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 alone, during or within one month of a myocardial infarction.

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

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has 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 indomethacin.

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.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Sildenafil: When amlodipine 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 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atrovastatin.

Digoxin: Co-administration of amlodipine 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 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 does not significantly alter the pharmacokinetics of ciclosporine.

Drug/Laboratory test interactions: None known.

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

4.6 Fertility, pregnancy and lactation
Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used.

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation.

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

The frequencies mentioned are subdivided on categories according to system organ class and frequency to following percentages:

Very common: more than 10%

Common: 10% or less, but more than 1%

Uncommon: 1%, or less, but more than 0,1%,

Rare: 0,1 % or less, but more than 0,01%

Very rare: 0,01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

Other reported side effects are:

Blood and the lymphatic system disorders

Very rare: thrombocytopenia, leucocytopenia

Immune system disorders

Very rare: allergic reaction

Metabolic and nutrition disorders

Very rare: hyperglycaemia

Psychiatric disorders

Uncommon: mood changes, insomnia

Nervous system disorders

Common: somnolence, dizziness, headache

Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia

Very rare: peripheral neuropathy

Eye disorders

Uncommon: visual disturbances

Ear and Labyrinth disorders

Uncommon: tinnitus

Cardiac disorders

Common: Palpitations

Rare: syncope

Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

Vascular disorders

Common: flushing

Uncommon: hypotension

Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, rhinitis

Very rare: coughing

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

Gastrointestinal disorders

Common: Abdominal pain

Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth

Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders

Very rare: abnormal liver function tests (mostly consistent with cholestasis), hepatitis, jaundice

Skin and subcutaneous tissue disorders

Uncommon: alopecia, pruritus, purpura, skin discolouration, increased sweating, rash

Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders

Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders

Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders

Uncommon: impotence, gynaecomastia

General disorders and administration site conditions

Common: oedema, fatigue

Uncommon: chest pain, asthenia, pain, malaise,

Investigations

Uncommon: increase or decrease in weight

4.9 Overdose

Available data suggest that gross over dosage 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.

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine over dosage 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 is highly protein-bound, dialysis is not likely to be of benefit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcium channel blockers – Dihydropyridine derivatives.

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.

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

SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

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 1mm 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.

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) 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.

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. In vitro 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

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose

based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Microcrystalline Cellulose, Sodium Starch Glycolate, Croscarmellose sodium, Crospovidone, Sodium Acid Citrate, Colloidal Anhydrous silica and Magnesium Stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and contents of container

S-Amlodipine Besilate Tablets 5 mg are supplied in box of 3 x 10's Blister Packing (Printed Aluminum Foil/ Amber Colour PVC film)

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SUMMARY OF PRODUCT CHARECTERISTICS OF S-AMLODIPINE BESILATE TABLETS 5 mg

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

Phillips Pharmaceuticals (Rwanda) Limited
GF 68, Kigali Modern City Market, Commercial Street,
B.P. 5671, Kigali, Rwanda.
E-mail: info@phillipsrwanda.com
Tel: +250 252 503841

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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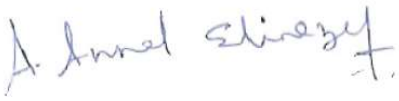
10. Date of revision of the text

28/01/2019

	Prepared & Checked by	Approved by
Name:	A. Annal Ebinezar	N. Thenmozhi
Signature:		
Designation:	Executive - Regulatory Affairs	Asst.Manager - Regulatory Affairs
Date:	28/01/2019	28/01/2019