1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

1. Name of the medicinal product

AMLODIPINE BESYLATE 10 MG TABLET USP

2. Qualitative and quantitative composition

Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tablet (mg)	Actual Qty/batch (kg)	Function
Dry Mixing					
1.	Amlodipine Besilate BP* eq. to Amlodipine	10.00	13.868	1.387	Anti-Hypertensive agent
2.	Microcrystalline Cellulose BP**	----	109.632	10.963	Diluent
3.	Pregelatinized Starch BP	----	35.000	3.500	Dry binder
4.	Colloidal anhydrous silica BP	----	0.500	0.050	Glidant
5.	Croscarmellose Sodium BP	----	5.000	0.500	Disintegrant
Blending & Lubrication					
6.	Magnesium Stearate BP	----	1.000	0.100	Lubricant
Total Weight of Uncoated Tablet			**165.00 mg**	**16.500 kg**	

*Quantity to be calculated on the basis of its potency.

Calculation of Amlodipine Besilate BP Eq. to Amlodipine 10 mg (100% Potency)

$$= \frac{\text{Label claim} \times \text{molecular weight of Amlodipine Besilate} \times 100}{(\text{Molecular Weight of Amlodipine}) \times \text{Potency}}$$

$$= \frac{10 \times 567.05 \times 100}{408.879 \times 100}$$

= 13.868 mg

**Quantity to be compensates on increasing quantity of active material

3. Pharmaceutical forms

Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

For the treatment of hypertension and chronic stable angina.

4.2 Posology and Method of administration

Posology

Adults

For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg 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.
Special populations

Elderly

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.

Paediatric population

Children and adolescents 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 .
Doses of amlodipine 2.5 mg are not possible with this medicinal product.
Children under 6 years old

Method of administration

Tablet for oral administration.

4.3 Contraindications

Amlodipine is contraindicated in patients with:
• Hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients
• 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 precaution for use

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

Patients with 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.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.
Use in patients with 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.
Use in elderly patients
In the elderly increase of the dosage should take place with care.
Use in renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable

4.5 Paediatric population

Not applicable

4.6 Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on amlodipine
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.
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.
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.
Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

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

4.7 Additional information on special populations

Not Applicable

4.8 Paediatric population

Not applicable

4.9 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.
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 .

4.10 Effects on ability to drive and use machines

Not known.

4.11 Undesirable effects

Adverse reaction to amlodipine:
Hives; difficulty breathing; swelling of your face, lips, tongue, or throat,
serious side effect such as:
Feeling like you might pass out;
Swelling in your hands, ankles, or feet;
Pounding heartbeats or fluttering in your chest; or
chest pain or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating
and general ill feeling.
Less serious amlodipine side effects may include:
headache; dizziness, drowsiness; tired feeling; stomach pain; flushing (warmth, redness or tingly feeling).

4.12 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: Anti-Hypertensive agent,

ATC Code: C08CA01

Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. It was widely accepted that DHP CCBs target L-type calcium channels, the major channel in muscle cells that mediate contraction; however, some studies have indicated that amlodipine also binds to and inhibits N-type calcium channels (see references in Targets section).
Similar to other DHP CCBs, amlodipine binds directly to inactive L-type calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives amlodipine additional arterial selectivity. At therapeutic sub-toxic concentrations, amlodipine has little effect on cardiac myocytes and conduction cells.

5.2 Pharmacokinetic Properties

Absorption:

Amlodipine is slowly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90%. Absorption is not affected by food.

Distribution:
The plasma protein binding of methylprednisolone in humans is approximately 97.5%.
Metabolism:
Hepatic. Metabolized extensively (90%) to inactive metabolites via the cytochrome P450 3A4 isozyme.
Elimination:
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

5.3 Preclinical Safety data

None stated.

6. Pharmaceutical Particulars

6.1 List of Excipients

Name of Material	Specification
Microcrystalline Cellulose	BP
Pregelatinized Starch	BP
Colloidal anhydrous silica	BP
Croscarmellose Sodium	BP
Magnesium Stearate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

10 X 10 Tablets in Alu-Alu Blister Pack

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

Name : Stallion Laboratories Pvt. Ltd.
Address :C-1B, 305/2, 3, 4& 5, G.I.D.C.
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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

STALLION LABORATORIES PVT. LTD. INDIA