

Summary of Product Characteristics
DIPMAR-10
(Amlodipine Besylate Tablets USP 10 mg)

1. Name of the medicinal product

DIPMAR-10 (Amlodipine Besylate Tablets USP 10 mg)

2. Qualitative / Quantitative composition

Each uncoated tablet contains Amlodipine Besylate USP Eq. to Amlodipine 10 mg.

Excipients of known effect:

Each uncoated tablet contains 55.80mg of Lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Uncoated Tablet

White Circular flat beveled edged uncoated tablet having breakline on one side and plain on other side of each tablet.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris
- Vasospastic (Prinzmetal's) angina

4.2 Posology and method of administration

Posology

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. 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. In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, Alpha blocker, beta blockers, or an angiotensin-converting enzyme inhibitors. No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients.

Shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis), unstable angina (excluding Prinzmetal's angina), severe hypotension, hemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

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

Summary of Product Characteristics
DIPMAR-10
(Amlodipine Besylate Tablets USP 10 mg)

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.

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

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 resulting in an increased risk of hypotension. 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).

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.

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.

Summary of Product Characteristics
DIPMAR-10
(Amlodipine Besylate Tablets USP 10 mg)

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.

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 atorvastatin.

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.

4.6 Fertility, pregnancy and lactation

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus. 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.

4.7 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 most commonly adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia.

Treatment: 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

Summary of Product Characteristics
DIPMAR-10
(Amlodipine Besylate Tablets USP 10 mg)

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). 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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

Not Applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Excipients	Specification
1.	Sodium Starch Glycolate	BP
2.	Lactose	BP

Summary of Product Characteristics
DIPMAR-10
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3.	Maize starch	BP
4.	Titanium Dioxide	BP
5.	PVPK 30	BP
6.	Methyl Paraben	BP
7.	Propyl Paraben	BP
8.	Isopropyl Alcohol	BP
9.	Magnesium Stearate	BP
10.	Talc	BP
11.	Croscarmellose sodium	BP
12.	Colloidal silicon dioxide	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at the temperature not exceeding 30°C. Protect from light and moisture.
Keep medicines out of reach of children.

6.5 Nature and contents of container

10 tablets are packed in one Alu-Pvc blister such 3 blisters are packed in a carton with insert.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:

ZAIN PHARMA LTD.

Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya

8. Marketing Authorization Number: Not Applicable

9. Date of First <Registration> / Renewal of The <Registration> Not Applicable

10. Date of Revision of the Text: