Shanur Healthcare (Pty) Ltd, 48/7.1/0037, AMLODIPINE DEZZO 5, Tablets, 5 mg

Shanur Healthcare (Pty) Ltd, 48/7.1/0038, AMLODIPINE DEZZO 10, Tablets, 10 mg

**Approved Professional Information for Medicines for Human Use:**

**AMLODIPINE DEZZO 5**

**AMLODIPINE DEZZO 10**

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

AMLODIPINE DEZZO 5 (5 mg) tablets

AMLODIPINE DEZZO 10 (10 mg) tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLODIPINE DEZZO 5 (5 mg) tablet:

Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine base.

Contains sugar: mannitol.

Each tablet contains 63 mg mannitol.

AMLODIPINE DEZZO 10 (10 mg) tablet:

Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine base.

Contains sugar: mannitol.

Each tablet contains 126 mg mannitol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets

AMLODIPINE DEZZO 5 (5 mg) tablets:

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White to off white, octagonal shaped, uncoated tablets, debossed with “AM 5” on one side and breakline on the other side. This breakline is non-functional. AMLODIPINE DEZZO 5 (5 mg) tablets should therefore not be broken.

AMLODIPINE DEZZO 10 (10 mg) tablets:
White to off-white, oval shaped, uncoated tablets, debossed with “AM 10” on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

AMLODIPINE DEZZO is indicated for the treatment of mild to moderate hypertension.
AMLODIPINE DEZZO may be combined with other antihypertensive medicines.
AMLODIPINE DEZZO is indicated for the treatment of angina pectoris.

### 4.2 Posology and method of administration

**Posology**

For both hypertension and angina, the usual initial dose is 5 mg AMLODIPINE DEZZO once daily which may be increased to a maximum dose of 10 mg depending on the individual patient’s response after 10 - 14 days therapy. AMLODIPINE DEZZO 5 (5 mg) tablets should not be broken even though they have a breakline.
No dose adjustment of AMLODIPINE DEZZO is required during combined administration of thiazide diuretics, beta blockers, or angiotensin converting enzyme inhibitors.

**Paediatric population**

Safety and efficacy in children have not been established.

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**Method of administration**

AMLODIPINE DEZZO is for oral use.

**4.3 Contraindications**

AMLODIPINE DEZZO is contraindicated in patients with:

- Hypersensitivity to amlodipine, dihydropyridines or any of the excipients listed in 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**

AMLODIPINE DEZZO should be used with caution in the elderly and patients with severe renal and liver impairment (see 5.2 Pharmacokinetic properties*).* These patients may need a lower dose.

*Hepatic impairment:*

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.

*Elderly*

In the elderly increase of the dosage should take place with care (see section 5.2).

*Renal impairment:*

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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.

The safety and efficacy of AMLODIPINE DEZZO have not been established in a hypertensive crisis.

*Use in heart failure:*

An increased incidence of pulmonary oedema has been reported. AMLODIPINE DEZZO may have a negative inotropic effect. The AUC of amlodipine may increase in patients with heart failure. Use AMLODIPINE DEZZO with caution in heart failure, severe hypotension, shock (including cardiogenic shock), or high grade aortic stenosis.

*Sodium*:

AMLODIPINE DEZZO contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free.'

Porphyria**:** Safety has not been established.

**Paediatric population**

Safety and efficacy in children have not been established.

**Excipient mannitol**

AMLODIPINE DEZZO contains mannitol which may have a laxative effect or cause diarrhoea.

**4.5 Interaction with other medicines and other forms of interaction**

AMLODIPINE DEZZO may be administered with thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines.

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**Effects of other medicinal products on amlodipine**

*CYP3A4 inhibitors:*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors such as protease inhibitors (e.g. ritonavir, indinavir, nefinavir), azole antifungals (e.g. ketoconazole, itraconazole, fluconazole), macrolides (e.g. erythromycin, clarithromycin), and verapamil or diltiazem may increase AMLODIPINE DEZZO exposure. Clinical monitoring and dose adjustment may 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).

CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin, phenobarbitone may reduce the effects of AMLODIPINE DEZZO.

Administration of AMLODIPINE DEZZO 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 coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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**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.

*Mechanistic Target of Rapamycin (mTOR) Inhibitors:*

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

*Simvastatin:*

Co-administration of multiple doses of 10 mg of AMLODIPINE DEZZO 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 DEZZO to 20 mg daily.

AMLODIPINE DEZZO may modify insulin and glucose response and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving AMLODIPINE DEZZO.

In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

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*Cyclosporine:*

Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciyclosporin. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

*Digoxin:*

Studies have indicated that the co-administration of amlodipine such as in AMLODIPINE DEZZO with digoxin did not change serum digoxin levels but AMLODIPINE DEZZO may reduce the renal clearance of digoxin.

*Cimetidine:*

Co-administration of cimetidine did not alter the pharmacokinetics of AMLODIPINE DEZZO.

*In vitro* data from studies with human plasma indicate that amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

**4.6 Fertility, pregnancy and lactation**

**Pregnancy and Breastfeeding**

Safety in pregnancy and lactation has not been established (see section 4.3)

**Fertility**

Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

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**4.7 Effects on ability to drive and use machines**

AMLODIPINE DEZZO may cause dizziness, headache and fatigue, the ability to react may be impaired which may affect your ability to drive or use machines. Caution is recommended especially at the start of treatment.

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**4.8 Undesirable effects**

**a) Summary of the safety profile**

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

**b) Tabulated list of adverse reactions**

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with amlodipine besilate.

| **System Organ Class** | **Frequency** | | |
|---|---|---|---|
| | **Frequent** | **Less Frequent** | **Not known** |
| Blood and lymphatic system disorders | | Leucopenia, thrombocytopenia | |
| Immune system disorders | | Hypersensitivity reactions | |
| Endocrine disorders | | Hyperglycaemia | |

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| | | | |
|---|---|---|---|
| Psychiatric disorders | | Insomnia, mood changes (including anxiety), depression and rarely confusion | |
| Nervous system disorders | Somnolence, dizziness, headache (especially at the beginning of treatment) | Tremor, dysgeusia, syncope, increased sweating, paraesthesia, hypoaesthesia, hypertonia, peripheral neuropathy | Extrapyramidal disorder |
| Eye disorders | Visual disturbance (including diplopia) | | |
| Ear and labyrinth disorders | | Tinnitus | |
| Cardiac disorders | Palpitations | Dysrhythmia (including ventricular tachycardia and atrial fibrillation), arrhythmia (including bradycardia), myocardial infarction | |
| Vascular disorders | Flushing | Hypotension, vasculitis | |
| Respiratory, thoracic and | Dyspnoea | Cough, rhinitis | |

| | | | |
|---|---|---|---|
| mediastinal disorders | | | |
| Gastrointestinal disorders | Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation) | Vomiting, dry mouth, pancreatitis, gastritis, gingival hyperplasia | |
| Hepatobiliary disorders | | Hepatitis, jaundice, and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine as contained in AMLODIPINE DEZZO. | |
| Skin and subcutaneous tissue disorders | | Alopecia, purpura, skin discolouration, hyperhidrosis, allergic reactions with pruritus, rash, exanthema, urticaria. Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson | Toxic Epidermal Necrolysis |

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| | | | |
|---|---|---|---|
| | | syndrome, Quincke oedema, photosensitivity | |
| Musculoskeletal and connective tissue disorders | Ankle swelling, muscle cramps | Arthralgia, myalgia, back pain | |
| Renal and urinary disorders | | Micturition disorder, nocturia, increased urinary frequency | |
| Reproductive system and breast disorders | | Impotence, gynaecomastia | |
| General disorders and administration site conditions | Oedema, fatigue, asthenia | Chest pain, pain, malaise | |
| Investigations | | Increased/decreased weight | |

**Reporting of suspected adverse reactions**

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

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**4.9 Overdose**

Symptoms:

Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24 – 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment:

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support. 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**

Category and Class: A.7.1 Vasodilators, hypotensive medicines.

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects

ATC Code: C 08 CA 01

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and smooth muscle without changing serum calcium concentrations.

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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 in experimental animals amlodipine reduces total ischaemic burden by the following action:

- Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Unloading of the heart reduces myocardial energy consumption and oxygen requirements.

Amlodipine binds to dihydropyridine binding sites. It has a minimal effect on cardiac conduction, contraction or heart rate.

**5.2 Pharmacokinetic properties**

**Absorption**

After oral administration of therapeutic doses, amlodipine is absorbed with peak blood levels between 6 - 12 hours post dose.

**Distribution**

The volume of distribution is approximately 20 l/kg.

**Biotransformation and Elimination**

Oral bioavailability is about 64 %. The terminal plasma elimination half-life is about 35 - 50 hours. Steady state plasma levels are reached after 7 - 8 days of consecutive dosing. Amlodipine is extensively metabolised by the liver with 90 % converted to inactive metabolites. 10 % of the parent compound and 60 % of the metabolites are excreted in the urine.

**Special populations**

*Use in the elderly*

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Elderly patients may have higher plasma concentrations of amlodipine than those in the younger patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance is decreased with resulting increases in AUC (approximately 40 - 60 %) and elimination half-life in elderly and hepatically insufficient patients. A similar increase in AUC was observed in patients with moderate to severe heart failure. Elderly patients should start on a lower dose of AMLODIPINE DEZZO.

*Use in renal failure*

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment. AMLODIPINE DEZZO may be used in such patients at normal doses. In patients with severe renal impairment, amlodipine dosages may need to be reduced. Amlodipine is not dialysable.

*Use in patients with impaired hepatic function*

Amlodipine half-life is prolonged in patients with impaired liver function.
AMLODIPINE DEZZO should therefore be administered at a lower (5 mg) initial dose in these patients.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Colloidal silica anhydrous

Magnesium stearate

Mannitol

Microcrystalline cellulose

Sodium starch glycolate

### 6.2 Incompatibilities

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Not applicable.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store in a cool, dry place at or below 30 °C. Protect from light and moisture.

Do not remove the blister from the carton until required for use.

### 6.5 Nature and contents of container

AMLODIPINE DEZZO 5 (5 mg) tablets and AMLODIPINE DEZZO 10 (10 mg) tablets are both packed in white, opaque PVC/PVDC-Aluminium foil blister strips [with VMCH (copolymer of vinyl chloride and vinyl acetate) heat seal coating] containing 10 tablets or 14 tablets in each pack size of 30 tablets or 28 tablets packed in an outer carton.

### 6.6 Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd.

Loch House, Unit 003,

3A Eton Road, Parktown,

Johannesburg, Gauteng, 2193

## 8. REGISTRATION NUMBERS

AMLODIPINE DEZZO 5 (5 mg) tablets: 48/7.1/0037

AMLODIPINE DEZZO 10 (10 mg) tablets: 48/7.1/0038

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## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 2016

## 10. DATE OF REVISION OF THE TEXT