Approved Professional Information for Medicines for Human Use:

AUSTELL AMLODIPINE 5 mg

AUSTELL AMLODIPINE 10 mg

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

AUSTELL AMLODIPINE 5 mg Tablets

AUSTELL AMLODIPINE 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTELL AMLODIPINE 5 mg Tablets

Each tablet contains amlodipine besylate equivalent to 5 mg amlodipine.

AUSTELL AMLODIPINE 10 mg Tablets

Each tablet contains amlodipine besylate equivalent to 10 mg amlodipine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

AUSTELL AMLODIPINE 5 mg Tablets

White to off-white, round, biconvex, uncoated tablets, with ‘5’ debossing on one side.

AUSTELL AMLODIPINE 10 mg Tablets

White to off-white, round, biconvex, uncoated tablets, with ‘10’ debossing on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

AUSTELL AMLODIPINE is indicated for the treatment of mild to moderate hypertension. AUSTELL AMLODIPINE may be combined with other antihypertensives medicines.

Coronary artery disease (CAD)

Angina pectoris

AUSTELL AMLODIPINE is indicated for the treatment of angina pectoris.

Chronic stable angina

AUSTELL AMLODIPINE is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. AUSTELL AMLODIPINE may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

AUSTELL AMLODIPINE is indicated to reduce the risk of coronary

revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease.

AUSTELL AMLODIPINE is also indicated to reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction, and to reduce the risk of stroke.

4.2 Posology and method of administration

Psology

Hypertension and Angina pectoris

The initial dose is 5 mg AUSTELL AMLODIPINE 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.

No dose adjustment of AUSTELL AMLODIPINE is required during combined administration of thiazide diuretics, beta-blockers, or angiotensin converting enzyme inhibitors.

Coronary artery disease

The recommended dosage range is 5 – 10 mg once daily. In reported clinical studies, the majority of patients required 10 mg.

Special populations

Use in the elderly

AUSTELL 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 (see section 4.4).

Use in patients with impaired hepatic function

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 (see sections 4.4). The pharmacokinetics of amlodipine, as in AUSTELL AMLODIPINE, have not been studied in severe hepatic impairment. AUSTELL AMLODIPINE should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Use in patients with renal failure

AUSTELL AMLODIPINE may be used in such patients at normal doses. Changes in plasma concentrations are not correlated with degree of renal impairment.

Paediatric population

The recommended antihypertensive oral dose in paediatric patients ages 6 – 17 years is 2,5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in paediatric patients.

The effect of AUSTELL AMLODIPINE on blood pressure in patients less than 6 years of age is not known.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients listed in section 6.1.
- Concomitant use with grapefruit juice (see section 4.5).
- 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

Concomitant use with potent cytochrome CYP3A4 medicines

The blood pressure lowering effect may be enhanced when potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir are co-administered (see section 4.5).

Use in the elderly

The time to reach peak plasma concentrations of amlodipine is variable and not significantly different between elderly and younger subjects.
Amlodipine clearance is decreased with resulting increases in AUC (40 – 60 %) and elimination half-life in elderly patients. AUC and elimination half-life in patients with congestive heart failure (CHF) were increased with age.
Elderly patients should start AUSTELL AMLODIPINE therapy at a lower dose.

Use in patients with renal failure

AUSTELL AMLODIPINE may be used at normal doses in patients with renal

impairment. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. In patients with severe renal impairment, AUSTELL AMLODIPINE doses may need to be reduced. Amlodipine is not dialysable.

Use in patients with impaired hepatic function

The half-life of amlodipine is prolonged in patients with impaired liver function. AUSTELL AMLODIPINE should therefore be administered at lower (5 mg) initial dose in these patients. 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 patients with heart failure

In a reported long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with New York Heart Association (NYHA) class 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.

4.5 Interaction with other medicines and other forms of interaction

Amlodipine has been administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral hypoglycaemic medicines.

In vitro data from reported studies with human plasma indicate that amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin,

warfarin, or indomethacin).

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone.

Grapefruit juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The reported study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of AUSTELL AMLODIPINE with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects (see section 4.3).

CYP3A4 inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) reportedly resulted in a 57 % increase in amlodipine systemic exposure and a significant further decrease in systolic blood pressure than with amlodipine alone.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine. AUSTELL AMLODIPINE should be used with caution when administered with CYP3A4 inhibitors (see

section 4.4).

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with AUSTELL AMLODIPINE. Close observation of patients is recommended when AUSTELL AMLODIPINE is co-administered with clarithromycin.

There is no information on the effect of the combination on the QT interval.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may decrease the plasma concentrations of amlodipine. AUSTELL AMLODIPINE should be used with caution when administered with CYP3A4 inducers.

Effects of medicines taken with AUSTELL AMLODIPINE

Cimetidine

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

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Digoxin

Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (alcohol)

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin

Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of amlodipine with ciclosporin increased the trough concentrations of ciclosporin and increased ciclosporin toxicity, from no change up to an average increase of 40 %. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine.

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of AUSTELL 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, AUSTELL AMLODIPINE may increase exposure of mTOR inhibitors.

Medicine/laboratory test interactions

None known.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are reportedly 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.

In reported clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential and their partners should be advised to ensure adequate contraceptive cover.

Pregnancy

The safety of AUSTELL AMLODIPINE in human pregnancy has not been established.

In reported animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

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 AUSTELL AMLODIPINE on infants is unknown.

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 a reported 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

a) Summary of the safety profile

The most frequently 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 reported clinical trials and postmarket spontaneous reports with amlodipine.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Leukocytopenia, thrombocytopenia.	
Immune system		Allergic reaction including pruritus,	

disorders		rash, angioedema and erythema multiforme.	
Metabolism and nutrition disorders		Hyperglycaemia.	
Psychiatric disorders		Insomnia, mood changes (including anxiety), depression. Confusion.	
Nervous system disorders	Somnolence, dizziness, headache (especially at the beginning of the treatment)	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia. Hypertonia, peripheral neuropathy, extrapyramidal disorder.	
Eye disorders		Visual disturbances (including diplopia).	
Ear and labyrinth disorders		Tinnitus.	
Cardiac disorders	Palpitations.	Myocardial infarction, arrhythmia	

		(including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain.	
Vascular disorders	Flushing.	Hypotension, Vasculitis.	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, rhinitis. Cough.	
Gastrointestinal disorders	Abdominal pain, nausea.	Vomiting, dyspepsia (including gastritis), altered bowel habits (including diarrhoea and constipation), dry mouth. Pancreatitis, gingival hyperplasia.	
Hepatobiliary disorders		Hepatitis, jaundice, hepatic enzymes elevations (mostly consistent with cholestasis).	
Skin and		Alopecia, purpura, skin discolouration,	

subcutaneous tissue disorders		hyperhidrosis, pruritus, rash, exanthema. Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.	
Musculoskeletal and connective tissue disorders	Ankle swelling.	Arthralgia, myalgia, muscle cramps, back pain.	
Renal and urinary disorders		Micturition disorder, nocturia, increased urinary frequency.	
Reproductive system and breast disorders		Impotence, gynecomastia.	
General disorders and administration site conditions	Oedema, fatigue.	Chest pain, asthenia, pain, malaise.	

Investigations		Weight increase, weight decrease.	

Paediatric population

Paediatric patients (ages 6 – 17 years)

Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

System Organ Class	**Undesirable effects**
Nervous system disorders	Headaches, dizziness
Vascular disorders	Vasodilation
Respiratory, thoracic, and mediastinal disorders	Epistaxis
Gastrointestinal disorders	Abdominal pain
General disorders and administration site conditions	Asthenia

Severe adverse events (predominantly headache) were reportedly experienced by 7,2 % with amlodipine 2,5 mg, 4,5 %

with amlodipine 5 mg, and 4,6 % with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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

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.

Treatment

Clinically significant hypotension due to AUSTELL AMLODIPINE overdosage may need active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

Non-cardiogenic pulmonary oedema has less frequently 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 is symptomatic and supportive. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after AUSTELL AMLODIPINE 10 mg ingestion has been shown to significantly decrease AUSTELL AMLODIPINE absorption. Activated

charcoal given 6 hours after AUSTELL AMLODIPINE had no effect.

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: C08CA01.

Mechanism of action

Amlodipine is a dihydropyridine, calcium ion influx inhibitor (calcium 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 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 exerts its activity by binding to the dihydropyridine binding sites. It exerts minimal action on cardiac conduction, contraction and heart rate.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is absorbed with peak plasma levels between 6 and 12 hours post dose. Absolute bioavailability has been estimated to be approximately 64 %. The volume of distribution is approximately 21 L/kg. Absorption of amlodipine is unaffected by consumption of a low-fat breakfast.

In vitro studies have shown that approximately 97,5 % of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination

A terminal plasma elimination half-life of 35 to 50 hours. Steady state, plasma concentrations are achieved after 7 to 8 days of consecutive dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites.

10 % of the parent compound and 60 % of the metabolites are excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate

Magnesium stearate

Microcrystalline cellulose

Silica Colloidal Anhydrous

Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in the original packaging. Protect from light.

6.5 Nature and contents of container

AUSTELL AMLODIPINE 5 mg Tablets:

Blister pack (Opaque PVDC coated PVC film and Aluminium foil) of 2, 4 or 6 blister strips each containing 14 tablets and 3 blister strips each containing 10 tablets.

AUSTELL AMLODIPINE 10 mg Tablets:

Blister pack (Opaque PVDC coated PVC film and Aluminium foil) of 2, 4 or 6 blister strips each containing 14 tablets and 3 blister strips each containing 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

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Parktown,

Johannesburg, 2193

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8. REGISTRATION NUMBERs

AUSTELL AMLODIPINE 5 mg: A39/7.1/0545

AUSTELL AMLODIPINE 10 mg: A39/7.1/0546

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 02 March 2007

10. DATE OF REVISION OF THE TEXT

30 January 2025