AMENDED PROPOSED PROFESSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

AMTAS 5 (Tablets)

AMTAS 10 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each AMTAS 5 mg tablet contains amlodipine besylate equivalent to 5 mg active amlodipine base.

Each AMTAS 10 mg tablet contains amlodipine besylate equivalent to 10 mg active amlodipine base.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

AMTAS 5: White to off-white, circular, biconvex, uncoated tablets plain on both sides.

AMTAS 10: White to off-white, circular, biconvex, uncoated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Hypertension

AMTASis indicated for the treatment of mild to moderate hypertension. AMTASmay be combined with other antihypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

AMTASis indicated for the treatment of angina pectoris.

Chronic stable angina

AMTASis 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. AMTASmay be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

AMTASis indicated to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease.

AMTASis 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

Posology

Hypertension and angina pectoris:

The usual initial dose for both hypertension and angina is 5 mg AMTASonce 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 AMTASis 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 clinical studies, the majority of patients required 10 mg.

Special populations

Use in elderly

The usual dosage regimens are recommended.

Use in patients with impaired hepatic function

AMTASshould be administered with caution in these patients (see section 4.4).

Use in renal failure

AMTASmay be used in such patients at normal doses. Changes in plasma concentrations are not correlated with degree of renal impairment (see section 4.4).

Paediatric population

Safety and effectiveness of AMTASin children have not been established.

Method of administration

For oral use.

4.3 CONTRA-INDICATIONS:

AMTASis contra-indicated in:

- patients with a known sensitivity to dihydropyridines, amlodipine, or any of the excipients (see section 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
- Concomitant use with grapefruit juice (see section 4.5)
- Safety of AMTASin human pregnancy or lactation has not been established.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Elderly patients may have higher plasma concentrations of amlodipine as in AMTASthan those in younger patients. The time to reach peak plasma concentrations of AMTASis similar in elderly and in younger subjects. AMTASclearance 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.

Use in renal failure

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

Use in patients with impaired hepatic function

The half-life of AMTASis prolonged in patients with impaired liver function. AMTASshould therefore be administered at lower (5 mg) initial dose in these patients. Caution is required, both during initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in heart failure

An increased incidence of pulmonary oedema has been reported. AMTASmay have a negative inotropic effect. AUC of AMTASmay increase in patients with heart failure.

Patients with heart failure should be treated with caution. 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 porphyria

Safety has not been established.

Paediatric population

Safety and effectiveness of AMTASin children have not been established.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

The blood pressure lowering effects of AMTASadds to the blood pressure-lowering effects of other medicines with antihypertensive properties.

AMTASmay 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.

Sublingual nitroglycerine: Concurrent administration of sublingual nitroglycerine, long-acting nitrates, beta blockers or other anti-anginal medicines with AMTASmay produce additive antihypertensive anti-anginal effects. Sublingual nitroglycerine may be used as needed to abort acute angina attacks during AMTAStherapy. Nitrate medication may be used during AMTAStherapy for angina prophylaxis. AMTASwill not protect against the consequences of abrupt beta blocker withdrawal; gradual beta blocker dose reduction is recommended.

Digoxin and warfarin: Studies have indicated that the co-administration of AMTASwith digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of [PRODUCT NAME].
In vitro data from studies with human plasma indicate that AMTAShas no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin or indomethacin).
The co-administration of AMTASdoes not significantly alter the effect of warfarin on prothrombin response time.

Ciclosporin: No interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. In renal transplant patients treated with

AMTASand ciclosporin, variable trough concentration increases (average 0 % - 40 %) of ciclosporin were observed. Consideration should therefore be given for monitoring ciclosporin levels in renal transplant patients on [PRODUCT NAME], and ciclosporin dose reductions should be made as necessary

CYP3A4 inhibitors: Concomitant use of AMTASwith strong or moderate CYP3A4 inhibitors (e.g. protease inhibitors, azole antifungals, macrolide antibiotics such as erythromycin or clarithromycin, verapamil or diltiazem) may give rise to a significant increase in amlodipine exposure resulting in an increased risk of hypotension, which may be more pronounced in the elderly. Clinical monitoring and dose adjustment may therefore be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on [PRODUCT NAME]. The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. AMTASshould therefore be used with caution together with CYP3A4 inducers.

Grapefruit: Administration of AMTASwith 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).

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse were observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to the risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as AMTASbe avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Tacrolimus: There is a risk of increased tacrolimus blood levels and toxicity when co-administered with AMTASbut the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of AMTASin patients treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Simvastatin: Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. The dose of simvastatin in patients on AMTASshould therefore be limited to 20 mg daily.

In clinical interaction studies, AMTASdid not affect the pharmacokinetics of atorvastatin.

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.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

In studies conducted with aluminium/magnesium (antacids) and sildenafil, there were no significant changes in the pharmacokinetics of amlodipine or the abovementioned medicines, when co-administered.

4.6 PREGNANCY AND LACTATION:

Women of childbearing potential

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

Pregnancy

The safety of AMTASin pregnancy has not been established.

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

Breastfeeding

Amlodipine is excreted in human milk. It's effect on infants is unknown. The safety of AMTASin breastfeeding has not been established.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AMTAScan affect the ability to drive and use machines. Dizziness, headache, fatigue or nausea may occur with [PRODUCT NAME]. Patients should exercise caution, especially at the start of treatment, before driving, operating hazardous machinery or performing any hazardous tasks.

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4.8 UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leucopoenia
Immune system disorders	Less frequent	Allergic reactions including pruritus, rash, angioedema and erythema multiforme
Endocrine disorders	Less frequent	Hyperglycaemia
Psychiatric disorders	Less frequent	Mood changes, depression, insomnia, confusion
Nervous system disorders	Frequent	Somnolence, dizziness, headache
	Less frequent	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy, extrapyramidal disorder
Eye disorders	Less frequent	Visual disturbances
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent	Palpitations
	Less frequent	Myocardial infarction, dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain
Vascular disorders	Frequent	Flushing
	Less frequent	Hypotension, vasculitis, syncope
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, rhinitis, cough
Gastro-intestinal disorders	Frequent	Abdominal pain, nausea, vomiting
	Less frequent	Altered bowl habits, dyspepsia, dry mouth, pancreatitis, gingival hyperplasia, gastritis

Hepato-biliary disorders	Less frequent	Hepatitis, jaundice, hepatic enzyme elevations
Skin and subcutaneous tissue disorders	Less frequent	Alopecia, purpura, skin discolouration, increased sweating, pruritus, rash, exanthema, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal, connective tissue and bone disorders	Frequent	Ankle swelling
	Less frequent	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	Less frequent	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
General disorders and administration site conditions	Frequent	Oedema, fatigue
	Less frequent	Asthenia, malaise, pain
Investigations	Less frequent	Weight increase, weight decrease

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “Adverse drug reaction and quality problem reporting form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

4.9 OVERDOSE

Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilation and possible 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.

Clinically significant hypotension due to AMTASoverdosage 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. 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.

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after amlodipine 10 mg ingestion has been shown to significantly decrease amlodipine absorption. Activated charcoal given 6 hours after amlodipine ingestion has no effect.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Category and class: A.7.1 Vasodilators, hypotensive, antihypertensive medicines including other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS etc.

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects; ATC code: C08 CA01

Amlodipine (besylate) is a dihydropyridine derivative.

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 vascular smooth muscle without changing serum calcium concentrations. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. In angina pectoris, 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. Oral bioavailability is about 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 and elimination

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose

Sodium starch glycolate

Disodium hydrogen citrate

Croscarmellose sodium

Crospovidone

Magnesium stearate

6.2. INCOMPATIBILITIES

Not applicable.

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6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 ˚C. Protect from light.

Keep blister in outer carton until before use.

6.5 NATURE AND CONTENTS OF CONTAINER

AMTAS5:

- Carton boxes containing 3 PVC/PVdC-Alu blister strips of 10 tablets each. The blister strips comprise forming foil as PVC film coated with PVdC and the lidding foil is hard tempered Alu-foil coated with a heat sealable lacquer.
- HDPE bottles consisting of PPCTC closure with wad having an induction sealing liner. Pack sizes of 250, 500 or 1000 tablets.

AMTAS10:

- Carton boxes containing 3 PVC/PVdC-Alu blister strips of 10 tablets each. The blister strips comprise forming foil as PVC film coated with PVdC and the lidding foil is hard tempered Alu-foil coated with a heat sealable lacquer.
- HDPE bottles consisting of PPCTC closure with wad having an induction sealing liner. Pack sizes of 250, 500 or 1000 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 31, Ground Floor,

Woodlands Office Park,

20 Woodlands Drive, Woodmead,

Johannesburg 2191

8. REGISTRATION NUMBERS

AMTAS 5: 41/7.1/0659 OR 41/7.1/0661

AMTAS 10: 41/7.1/0660 OR 41/7.1/0662

9. DATE OF FIRST AUTHORISATION

Date of registration: 09 June 2016

10. DATE OF REVISION OF THE TEXT

09 June 2016

21 November 2024