SCHEDULING STATUS **S3**

PROPRIETARY NAME (AND DOSAGE FORM)

AMLATE 5 (tablet)

AMLATE 10 (tablet)

COMPOSITION

AMLATE 5: Each tablet contains amlodipine maleate equivalent to 5 mg amlodipine base. Sugar free.

AMLATE 10: Each tablet contains amlodipine maleate equivalent to 10 mg amlodipine base. Sugar free.

The inactive ingredients of **AMLATE 5** and **AMLATE 10** tablets are magnesium stearate, microcrystalline cellulose, silica colloidal anhydrous and sodium starch glycolate.

PHARMACOLOGICAL CLASSIFICATION

A 7.1 Vasodilators, hypotensive medicines

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Amlodipine is a dihydropyridine calcium ion channel blocker. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without affecting serum calcium concentrations. Direct relaxation of vascular smooth muscle forms the basis of the antihypertensive action.

In angina pectoris, amlodipine acts as a peripheral arteriolar vasodilator resulting in a reduction in total peripheral resistance (afterload). Myocardial energy and oxygen requirements are reduced. Amlodipine exerts its activity by binding to the dihydropyridine binding sites. It exerts minimal action on cardiac conduction, contraction and heart rate.

Pharmacokinetic properties:

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 to 12 hours. Amlodipine has a bioavailability of about 64 % and a plasma elimination half-life of 35 to 50 hours, allowing for once-daily oral dosing. Steady state plasma concentrations are achieved after 7 to 8 days of consecutive dosing. The volume of distribution is about 20 ℓ/kg.

Metabolism is via the liver and is extensive with less than 10 % of amlodipine appearing unchanged in the urine. Metabolites are inactive and primarily (up to 60 %) excreted via the kidney.

INDICATIONS

AMLATE is indicated for:

- The treatment of angina pectoris
- The treatment of mild-to moderate hypertension, alone or in combination with other antihypertensives

CONTRA-INDICATIONS

Hypersensitivity to amlodipine, other dihydropyridines or to any of the excipients.

Pregnancy and lactation.

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.

WARNINGS AND SPECIAL PRECAUTIONS

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

Use in the elderly

Amlodipine clearance is decreased (40-60 %) in the elderly, which results in increased amlodipine concentrations in the area under the concentration-time curve (AUC) and elimination half-life.

Therefore, elderly patients should start **AMLATE** therapy at a lower dose.

Use in renal failure

Although amlodipine is excreted primarily via the kidney, mild renal impairment does not appear to have an effect on the plasma concentrations.

Severe renal impairment may however require a dosage reduction.

Amlodipine is not dialysable.

Use in impaired hepatic function

The half-life of amlodipine is significantly prolonged in patients with impaired hepatic function.

AMLATE should therefore be administered at lower doses in these patients.

Use in children

Safety and efficacy has not been established.

Use in heart failure

Patients with heart failure should be treated with caution.

An increased incidence of pulmonary oedema has been reported.

AMLATE may have a negative inotropic effect. AUC of amlodipine may increase in patients with heart failure.

Calcium channel blockers, including **AMLATE**, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Porphyria

Safety has not been established.

Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis.

Increased angina or myocardial infarction

Exacerbation of angina and acute myocardial infarction can develop after starting or increasing the dose of **AMLATE**, particularly in patients with severe obstructive coronary artery disease.

Beta-blocker withdrawal

Amlodipine will not protect against the consequences of abrupt beta-blocker withdrawal; gradual beta-blocker dose reduction is recommended.

Effects on ability to drive and use machines

AMLATE can have minor or moderate influence on the ability to drive and use machines. If patients taking **AMLATE** suffer from dizziness, headache, fatigue or nausea their ability to react may be impaired. Caution is recommended especially at the start of treatment.

INTERACTIONS

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 **AMLATE** be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Administration of **AMLATE** with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Amlodipine is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4, and interactions may occur with other medicines, such as quinidine, sharing the same metabolic pathway. In one study, quinidine appeared to inhibit nifedipine (a calcium-channel blocker) metabolism resulting in increased serum concentrations of nifedipine; quinidine concentrations were unchanged. However, conflicting effects on serum-quinidine concentrations have been reported.

Concomitant use of **AMLATE** with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals (ketoconazole, itraconazole, voriconazole), macrolides like erythromycin or clarithromycin, verapamil, diltiazem and ritonavir) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

There are no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericum perforatum, carbamazepine, phenytoin) may give a lower plasma concentration of amlodipine. The effects of dihydropyridine calcium-channel blockers such as **AMLATE** may be reduced by enzyme-inducing antiepileptics such as carbamazepine, phenobarbital, and phenytoin. In contrast, sodium valproate has been reported to increase plasma-nimodipine (a calcium-channel blocker) concentrations.

AMLATE should be used with caution together with CYP3A4 inducers.

The blood pressure lowering effects of **AMLATE** adds to the blood pressure-lowering effects of other medicines with antihypertensive properties. Enhanced antihypertensive effects may be seen if **AMLATE** is used with medicines such as antipsychotics that cause hypotension. Procainamide may enhance the effects of antihypertensives.

There is a risk of increased tacrolimus blood levels when co-administered with **AMLATE** but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of **AMLATE** in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

No interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients, where variable trough concentration increases (average 0 % - 40 %) of ciclosporin were observed. Consideration should be given to monitoring ciclosporin levels in renal transplant patients on **AMLATE**, and ciclosporin dose reductions should be made as necessary.

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.

Lithium neurotoxicity has been reported during co-administration of lithium and the calcium-channel blockers verapamil or diltiazem. Concurrent use of lithium with **AMLATE** potentially may result in neurotoxicity in the form of nausea, vomiting, diarrhoea, ataxia, tremors, and/or tinnitus; caution is recommended.

Concurrent administration of sublingual nitroglycerin, long acting nitrates, beta-blockers or other antianginal agents with **AMLATE** may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during **AMLATE** therapy. Nitrate medication may be used during **AMLATE** therapy for angina prophylaxis.

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

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

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

Studies have indicated that the co-administration of amlodipine with digoxin did not change the serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine.

PREGNANCY AND LACTATION

AMLATE is contraindicated in pregnancy and lactation (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

Hypertension and Angina Pectoris

Adults:

An initial dose of 5 mg **AMLATE** once daily is recommended, which may be increased to a maximum dose of 10 mg once a day, after 10-14 days of therapy if there is no improvement.

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

Although no “rebound effect” has been reported upon discontinuation of **AMLATE**, a gradual decrease of dosage with medical practitioner supervision is recommended.

Renal impairment

In patients with mild renal impairment, **AMLATE** may be used at normal doses.

In patients with severe renal impairment, **AMLATE** dosages may need to be reduced.

Liver impairment

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

Elderly patients

Elderly patients should start **AMLATE** therapy at a lower dose.

SIDE EFFECTS

Blood and the lymphatic system disorders

Less Frequent: Thrombocytopenia, leucopenia, blood dyscrasias, haemorrhagic complications in surgical patients

Immune system disorders

Less Frequent: Allergic reactions, angioedema, erythema multiforme

Metabolism and nutrition disorders

Less Frequent: Hyperglycaemia

Psychiatric disorders

Less Frequent: Depression, mood changes (including anxiety), insomnia, confusion

Nervous system disorders

Frequent: Dizziness, headache, somnolence

Less Frequent: Hypertonia, hypoaesthesia/paraesthesia, peripheral neuropathy, syncope, tremor, dysgeusia

Eye disorders

Frequent: Visual disturbance (including diplopia)

Ear and labyrinth disorders

Less Frequent: Tinnitus

Cardiac disorders

Frequent: Palpitations

Less Frequent: Myocardial infarction, dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular disorders

Frequent: Flushing

Less Frequent: Hypotension (including orthostatic hypotension), vasculitis

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea

Less Frequent: Coughing, rhinitis

Gastrointestinal disorders

Frequent: Nausea, abdominal pain, dyspepsia, altered bowel habits (including diarrhoea and constipation)

Less Frequent: Vomiting, gingival hyperplasia, pancreatitis, gastritis, dry mouth

Hepato-biliary disorders

Less Frequent: Hepatitis, jaundice, raised liver enzymes (mostly consistent with cholestasis)

Skin and subcutaneous tissue disorders

Less Frequent: Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria

Musculoskeletal, connective tissue and bone disorders

Frequent: Ankle swelling, muscle cramps

Less Frequent: Arthralgia, myalgia, back pain

Renal and urinary disorders

Less Frequent: Increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders

Less Frequent: Gynaecomastia, impotence

General disorders and administration site conditions

Frequent: Oedema, peripheral oedema, fatigue, asthenia

Less Frequent: Chest pain, pain, malaise

Investigations

Less Frequent: Weight increased, weight decreased

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

Clinically significant hypotension due to **AMLATE** overdosage requires 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 of benefit in reversing the effects of calcium channel blockade. 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.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

IDENTIFICATION

AMLATE 5: White to off-white, round, flat, beveled edged, uncoated tablets, embossed "R" on one side and "177" on the other side.

AMLATE 10: White to off-white, oval, biconvex, uncoated tablets, embossed "R" on one side and "178" on the other side.

PRESENTATION

30, 90, 100, 300 and 500 tablets packed in white HDPE bottles with white caps and inclusion of a silica gel container.

Blister packs of 28 tablets (2 blister strips of 14 tablets each) or 30 tablets (3 blister strips of 10 tablets each) are available.

28's blister packs: The tablets are packed into blister strips composed of either silver coloured aluminium foil / silver coloured cold formable foil or peelable white paper backed aluminium foil / silver coloured cold formable foil. The blister strip/s are packed into a unit carton.

30's blister packs: The tablets are packed into blister strips composed of peelable white paper backed aluminium foil / silver coloured cold formable foil. The blister strip/s are packed into a unit carton.

STORAGE INSTRUCTIONS

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

Keep the bottle well closed.

Keep tablets in the original container.

Keep the blisters in the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

REGISTRATION NUMBERS

AMLATE 5: A40/7.1/0312

AMLATE 10: A40/7.1/0313

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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