APOTEX NZ LTD

NEW ZEALAND DATA SHEET

APO- AMLODIPINE

1. PRODUCT NAME

APO-AMLODIPINE (2.5mg, 5mg and 10mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5mg tablet contains amlodipine besilate equivalent to 2.5mg amlodipine.

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

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

Excipient(s) of known effect
APO-AMLODIPINE contain lactose.
APO-AMLODIPINE does not contain gluten

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-AMLODIPINE 2.5mg are white to off-white, round unscored tablets, engraved “APO” on one side and “AML” over “2.5” on the other side. Each tablet typically weighs 45mg. Do not halve tablet.

APO-AMLODIPINE 5mg are white to off-white, round, scored tablets, engraved “APO” on one side and “AML” over scored “5” on the other side. Each tablet typically weighs 90mg

APO-AMLODIPINE 10mg are white to off-white, round unscored tablets, engraved “APO” on one side and “AML” over “10” on the other side. Each tablet typically weighs 180mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amlodipine is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit for the addition of amlodipine, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.

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.

Amlodipine may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine may be used alone as monotherapy, or in combination

with other antianginal drugs in patients with angina that is refractory to nitrates and/or beta blockers.

4.2 Dose and method of administration

For both hypertension and angina, the usual initial dose of APO-AMLODIPINE is 5mg once daily. This may be increased to a maximum dose of 10mg per day depending on the individual patient's response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Elderly
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore, normal dosage regimens are recommended.

Renal Impairment
Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. Amlodipine may be used at normal doses in patients with renal failure. Amlodipine is not dialysable.

Paediatric population
Amlodipine is not recommended for use in children.

4.3 Contraindications

Amlodipine is contraindicated in patients with a known sensitivity to amlodipine, other dihydropyridines or any of the inactive ingredients.

4.4 Special Warnings and Precautions for use

Patients with Heart Failure
In a 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-ishaemic 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 (refer to section 5.1 Pharmacodynamic Properties– *Patients with Heart Failure*).

Hepatic Impairment
As with all calcium channel blockers, amlodipine's half-life is prolonged in patients with impaired liver function and the dosage recommendations have not been established. The compound should therefore be administered with caution in these patients.

Paediatric Use
Safety and effectiveness of amlodipine in children have not been established.

4.5 Interactions with other medicines and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, alpha blockers, ACE inhibitors, long acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory agents, antibiotics, and oral hypoglycaemic agents.

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

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. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Grapefruit Juice: Administration of amlodipine with grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

CYP3A4 Inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients, the plasma concentration of amlodipine was increased. The clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution when administered with CYP3A4 inhibitors.

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

CYP3A4 Inducers: There are no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hyoericum perforatum* (St John's Wort)) may decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution and when administered with CYP3A4 inducers.

Special studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine 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 100mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetics parameters of amlodipine. 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 10mg doses of amlodipine with 80mg atorvastatin resulted in no significant changes 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 healthy volunteers.

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

Warfarin: Co-administration of amlodipine and warfarin did not change the warfarin prothrombin response time.

Cyclosporin: No drug interaction studies have been conducted with cyclosporin 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 cyclosporin affects the trough concentrations of cyclosporin, from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. 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. Concomitant use of mTOR inhibitors and amlodipine may increase exposure of mTOR inhibitors.

4.6 Fertility, pregnancy and lactation

Fertility

There was no effect on the fertility of rats treated with amlodipine.

Pregnancy

Category C

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine did not demonstrate and fetotoxic or teratogenic potential in animal reproductive studies other than delay in parturition and prolongation of labour in rats at a dose level fifty times the maximum recommended dose in humans. No mutagenic activity has been found in tests for gene mutations of cytogenic assays. Accordingly, use in pregnancy is recommended only when there is no safer alternative and when disease itself carries greater risk for the mother and fetus.

Lactation

Experience in humans indicates that amlodipine is transferred into human breast milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy-induced hypertension was 0.85 following amlodipine administration at an initial dose of 5mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6mg and 98.7 mcg/kg, respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 mcg/kg.

4.7 Effects on ability to drive and use machinery

Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed adverse effects were:

MedDRA System Organ Class	**Undesirable Effects**
Nervous System Disorders	Headache, dizziness, somnolence
Cardiac Disorders	Palpitations
Vascular Disorders	Flushing
Gastrointestinal Disorders	Abdominal pain, nausea
General Disorders and Administration Site Conditions	Oedema, fatigue

In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed adverse effects in marketing experience include:

MedDRA System Organ Class	**Undesirable Effects**
Blood and Lymphatic System Disorders	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	Hyperglycaemia
Psychiatric Disorders	Insomnia, mood changes
Nervous System Disorders	Hypertonia, hypoesthesia/paresthesia, Peripheral neuropathy, syncope, taste perversion, tremor, extrapyramidal disorder
Eye Disorders	Visual Disturbances
Ear and Labyrinth Disorders	Tinnitus

Vascular Disorders	Hypotension, vasculitis
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, rhinitis
Gastrointestinal Disorders	Altered bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Tissue Disorders	Alopecia, increased sweating, purpura, skin discolouration, urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle cramps, myalgia
Renal and urinary Disorders	Increased urinary frequency, micturition disorder, nocturia
Reproductive System and Breast Disorders	Gynaecomastia, impotence
General Disorders and Administration Site Conditions	Asthenia, malaise, pain
Investigations	Weight increase/decreases

Rarely, allergic reactions including pruritic, rash, angioedema and erythema multiforme, and have been reported.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently, and (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation and chest pain.

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 https//nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Available data suggest that overdose might be expected to cause excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonist. Hypotension and bradycardia are usually seen within 1 to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist up to 7 days. Marked and probably prolonged systemic hypotension, up to and including shock with fatal outcome have been reported.

Reports of intentional overdose include a patient who ingested 250 mg and was asymptomatic and was not hospitalised; another (120 mg) was hospitalised, underwent gastric lavage and remained normotensive; a third one (105 mg) was hospitalised and had hypotension (90/50 mmHg) which normalised following plasma expansion. Death resulted from a mixed overdose of 140 mg and 10 mefenamic acid capsules in a 15-year old girl, and from a mixed overdose of amlodipine 70 mg and an unknown quantity of oxazepam in a 63-year old woman. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support, including elevation of the extremities, and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecacemesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Dialysis is not likely to be of benefit since amlodipine is highly proteinbound.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects; ATC code: C08CA01

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.

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:

1. Amlodipine dilates the 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.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. The dilatation increases the myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina) and blunts smoking-induced coronary vasoconstriction.

In patients with hypertension, once-daily dosing provides clinically significant reductions in 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.

In patients with angina, once-daily administration of amlodipine increases total exercise time, time to angina onset and time to 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

Patients with Heart Failure
Haemodynamic studies and exercise-based controlled clinical trial in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA class III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure compared to placebo (refer to section 4.4 *Special Warnings and Precautions for Use*).

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes and gout.

5.2 Pharmacokinetics Properties

Absorption:
Amlodipine is well absorbed orally with peak blood levels occurring between 6 and 12 hours post-dose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64% (range 52% to 88%). The volume of distribution is approximately 20 L/kg. The absorption of amlodipine is unaffected by consumption of

food. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/Elimination:
The terminal plasma elimination half-life is about 35 to 50 hours and is consistent with once daily dosing. Steady-state plasma levels are reached after 7 to 8 days of consecutive 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.

Amlodipine is not dialysable.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25°C. Protect from heat light and moisture.
Keep container tightly closed.

6.5 Nature and contents of container

Bottles of 100, 250 and 500 and blisters of 120 for 5mg and 10mg tablets
Bottles of 100 for 2.5mg tablets

Not all strengths and pack sizes may be available

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd
32 Hillside Road
Glenfield
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

9. DATE OF FIRST APPROVAL

Apo-Amlodipine 2.5mg – 27 May 2010
Apo-Amlodipine 5mg, 10mg – 21 December 2006

10. DATE OF REVISION OF THE TEXT

10 September 2018

Summary Table of Changes

Section changed	Summary of new information
2 & 3	Minor editorial change
4.2, 4.3, 4.4, 4.6, 4.7,4.8, 4.9, 5.1, 5.2 & 5.3	Updated as per latest approved information.
4.5	Additional safety related data as per latest approved information.