New Zealand Data Sheet

1 PRODUCT NAME

Vasorex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amlodipine besilate 2.5 mg, 5 mg and 10 mg tablets

3 PHARMACEUTICAL FORM

Vasorex 2.5 mg tablets are white to off white, round with “C” debossed on one side and “126” on the other side. Alternatively, they are debossed on one side with “3235” and “WPI” on the other side. Each tablet contains amlodipine besilate equivalent to 2.5 mg of amlodipine.

Vasorex 5 mg tablets are white to off white, round with “C” debossed on one side and “127” on the other side. Alternatively, they are debossed on one side with “3236” and “WPI” on the other side. Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine.

Vasorex 10 mg tablets are white to off white, round with “C” debossed on one side and “128” on the other side. Alternatively, they are debossed on one side with “3237” and “WPI” on the other side. Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

Do not halve the tablet as dose equivalence when the tablet is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vasorex 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 from the addition of amlodipine, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

Vasorex 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.

Vasorex may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Vasorex 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

Treatment for Angina and Hypertension
The common initial dose for amlodipine is 5 mg once per day.

The dose may be increased to 10 mg (maximum dosage) dependent on the patient's response to the medication.

Do not halve the tablet as dose equivalence when the tablet is divided has not been established.

Amlodipine does not require the dose to be modified when administered alongside angiotensin-converting enzyme inhibitors, beta blockers and thiazide diuretics.

Use in Elderly
For both elderly and younger patients, the time to attain amlodipine peak plasma concentrations is comparable. In elderly patients, the clearance of amlodipine reduces with increases to both elimination half-life and AUC.

For congestive heart failure patients, AUC and elimination half-life increases, as anticipated for this age group.

Amlodipine is well tolerated when administered in both elderly and young patients when used at comparable doses. Therefore, a normal dose schedule is recommended.

Use in Renal Disease
Amlodipine is metabolised extensively to its inactive metabolites with the unchanged molecule being excreted (10%) via the urine. There is no correlation between the variations in amlodipine plasma concentrations and renal impairment degree. Therefore, amlodipine can be used in renally impaired patients at normal doses.

Use in Children
Vasorex tablets are not suitable for children.

4.3 Contraindications

Vasorex tablets are not to be used in individuals with identified hypersensitivity to amlodipine or to any of the excipients (Please refer to section 6.1 Pharmaceutical Particulars, List of Excipients).

4.4 Special warnings and precautions for use

Use in Individuals with Heart Failure
An increase of pulmonary oedema reports in patients taking amlodipine with New York Heart Association (NYHA) classes III and IV heart failure of non-ischaemic aetiology has been observed in the PRAISE-2 study (a long-term placebo-controlled study). The incidence of deteriorating heart failure was not significantly different when evaluated against placebo (Please refer to section 5.1 Pharmacodynamic Properties, Use in Individuals with Heart Failure).

Use in Individuals with Hepatic Impairment
In individuals with hepatic impairment, the half-life of amlodipine (and other calcium channel blockers) is extended and modifications to the amlodipine dosage are yet to be determined in these patients. Caution should be taken when using amlodipine in patients who have impaired liver function.

Use in Children
Vasorex tablets are not recommended for children as safety and effectiveness has not been determined.

4.5 Interaction with other medicines and other forms of interaction

Amlodipine can be safely given alongside alpha blockers, angiotensin-converting enzyme inhibitors, antibiotics, beta blockers, long-acting nitrates, non-steroidal anti-inflammatory agents, oral hypoglycaemic agents, sublingual glyceryl trinitrate, and thiazide diuretics.

Information from *in vitro* human plasma studies suggest that amlodipine has no protein bound effect on the medicines examined, for example; digoxin, indomethacin, phenytoin or warfarin.

Clarithromycin: Clarithromycin is a CYP3A4 inhibitor. Individuals taking both amlodipine and clarithromycin have a higher risk of hypotension. Careful monitoring is recommended for patients taking amlodipine with clarithromycin.

CYP3A4 Inducers: There is no information in regard to the effect on amlodipine with the use of CYP3A4 inducers. The use of CYP3A4 inducers, for example Hypericum perforatum (St John's Wort) and rifampicin with amlodipine may result in a reduction of amlodipine plasma concentrations. Caution should be taken when amlodipine is used with CYP3A4 inducers.

CYP3A4 Inhibitors: Combination therapy of amlodipine with erythromycin (CYP3A4 inhibitor) in younger patients and diltiazem in aged patients, results in an increase of amlodipine plasma concentration. The clinical significance of this conclusion is unknown. Therefore, strong CYP3A4 inhibitors, for example; itraconazole, ketoconazole and ritonavir may result in an increase of amlodipine plasma concentrations to a larger degree than diltiazem. Caution should be taken when amlodipine is used with CYP3A4 inhibitors.

Grapefruit Juice: The consumption of grapefruits or grapefruit juice when taking amlodipine is not recommended. Some individuals may experience increased bioavailability, causing an increase in blood pressure decreasing effects.

Simvastatin: Combination therapy of amlodipine (10 mg, multiple doses) with simvastatin (80 mg) resulted in an increase of simvastatin exposure of 77% in comparison to simvastatin monotherapy. For patients on amlodipine, the simvastatin dosage should be limited to 20 mg per day.

Special Studies: The Effect of Added Medications on Amlodipine
Aluminium/Magnesium (Antacid): Amlodipine pharmacokinetics were not significantly affected when an individual dose of amlodipine was co-administered with an aluminium/magnesium antacid.

Cimetidine: Amlodipine pharmacokinetics were not changed when amlodipine was co-administered with cimetidine.

Sildenafil: Amlodipine pharmacokinetics were not affected when amlodipine was co-administered with an individual sildenafil dose of 100 mg in patients with essential hypertension. Combination therapy of amlodipine and sildenafil, results in each drug individually utilising its own reducing effect on blood pressure.

Special Studies: The Effect of Amlodipine on Added Medications

Atorvastatin: Atorvastatin pharmacokinetic steady state parameters were not significantly modified when atorvastatin (80 mg) was administered in combination with amlodipine (multiple doses, 10 mg).

Cyclosporin: For the combination therapy of cyclosporin and amlodipine there are no drug interaction studies completed in healthy individuals or additional populations. The only studies available are on renal transplant patients. The studies report that combination therapy of cyclosporin with amlodipine affects the cyclosporin trough concentrations, from no difference to an increase of 40% on average. Cyclosporin levels should be monitored in renal transplant patients that are also taking amlodipine.

Digoxin: There was no difference to the renal clearance or serum levels of digoxin when administered in combination with amlodipine in healthy individuals.

Ethanol (Alcohol): There was no significant change to the ethanol pharmacokinetics when administered with amlodipine (individual dose and multiple doses, 10 mg).

mTOR (Mechanistic Target of Rapamycin) Inhibitors: mTOR inhibitors are substrates of CYP3a, for example, everolimus, sirolimus and temsirolimus. Amlodipine is considered a weak CYP3A inhibitor. An increased exposure of mTOR inhibitors may occur with the use of amlodipine.

Tacrolimus: Combination therapy of tacrolimus with amlodipine may increase tacrolimus blood levels. To avoid tacrolimus toxicity, amlodipine administration requires careful observation of tacrolimus blood levels and if appropriate, an adjustment of dosage of tacrolimus.

Warfarin: There was no change to the warfarin prothrombin response time when administered in combination with amlodipine.

4.6 Fertility, pregnancy and lactation

Fertility

No fertility effects were observed in rats that were administered amlodipine.

Use in pregnancy

Category C.

It has not been established whether amlodipine is safe to use in human pregnancy or while breastfeeding. Rats treated with amlodipine at a dosage fifty times more than the recommended human maximum dose, showed no teratogenic or foetotoxic capacity in animal reproductive studies conducted. There were reports of amlodipine delaying birth and extending labour. Tests completed for cytogenic assays and gene mutations have

shown no mutagenic activity. The use of amlodipine in pregnancy is only recommended if the disease is a greater risk to the mother and baby and there is no other alternative.

Breastfeeding
Women should be advised to not breastfeed when taking Vasorex tablets as it is known that amlodipine is passed through into the breast milk. In 31 women who were breastfeeding and presented with hypertension that was pregnancy-induced, the amlodipine median concentration ratio of milk to plasma was 0.85. This result was after the administration of amlodipine at 5 mg once per day (initial dosage) which was modified as required (mean daily dose of 6 mg and body weight adjusted daily dose of 98.7 mcg/kg). The projected amlodipine daily dose in the child through breastfeeding was 4.17 mcg/kg.

4.7 Effects on ability to drive and use machines

There are no likely effects from the use of amlodipine that may impair the ability for a patient to drive or use machines.

4.8 Undesirable effects

Amlodipine is tolerated well. The most common adverse effects observed with individuals experiencing angina or hypertension in placebo-controlled clinical trials were:

MedDRA System Organ Class	**Description of Adverse Reaction**
Cardiac Disorders	Palpitations
Gastrointestinal Disorders	Nausea and pain in the abdomen
General Disorders and Administration Site Conditions	Fatigue and oedema
Nervous System Disorders	Dizziness, headache and somnolence
Vascular Disorders	Flushing

No association to amlodipine abnormalities from clinically significant laboratory tests were detected in these clinical studies.

Based on marketing knowledge, less common adverse effects observed are:

MedDRA System Organ Class	**Description of Adverse Reaction**
Blood and Lymphatic System Disorders	Leucopenia and thrombocytopenia
Ear and Labyrinth Disorders	Tinnitus
Eye Disorders	Disturbances to vision
Gastrointestinal Disorders	Changes to bowel habits, pancreatitis, dry mouth, dyspepsia (incorporating gastritis), gingival hyperplasia and vomiting
General Disorders and Administration Site Conditions	Asthenia, pain and malaise
Investigations	Increase in weight and decrease in weight
Metabolism and Nutrition Disorders	Hyperglycaemia
Musculoskeletal and Connective Tissue Disorders	Arthralgia, cramps in the muscle, back pain and myalgia
Nervous System Disorders	Extrapyramidal disorder, hypoesthesia/paresthesia, peripheral

	neuropathy, hypertonia, syncope, taste perversion and tremor
Psychiatric Disorders	Changes to mood and insomnia
Renal and Urinary Disorders	Micturition disorder, nocturia and urine frequency increased
Reproductive System and Breast Disorders	Impotence and gynaecomastia
Respiratory, Thoracic and Mediastinal Disorders	Cough, rhinitis and dyspnoea
Skin and Subcutaneous Tissue Disorders	Alopecia, discoloration of the skin, increase in sweating, purpura and urticaria
Vascular Disorders	Hypotension and vasculitis

There have been rare reports of allergic reactions, for example; angioedema, erythema multiforme, pruritis and rash.

There have been infrequent reports of hepatic enzyme increases, hepatitis and jaundice which are consistent with cholestasis. In some circumstances, due to the associated amlodipine use, hospitalisation was required due to the severity of the adverse effects. However, in most cases, it is undefined whether a causal association is apparent.

Adverse effects such as arrhythmia (atrial fibrillation, bradycardia and ventricular tachycardia), chest pain and myocardial infarction have been rarely reported. This is consistent with adverse effects associated with other calcium channel blockers and cannot be set apart from the underlying disease history.

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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Signs and symptoms

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.

Accessible information implies that overdosage of amlodipine may be predicted to cause peripheral vasodilatation that is considered excessive with marked hypotension and reflex tachycardia. Following an overdose, dysrhythmias may arise (as seen with other calcium antagonists). Bradycardia and hypotension can usually be observed following overdose within one to five hours. Even with treatment, hypotension can continue for more than 24 hours. Reports have shown that cardiac rhythm disturbances may continue for up to seven days. There have also been reports of marked and most likely prolonged systemic hypotension up to and incorporating shock with an outcome of death.

Amlodipine Overdose Reports

Dosage Taken	Overdose Notes
30 mg amlodipine (accidental overdose)	19-month-old male patient consumed approximately 2 mg/kg amlodipine and required emergency hospitalisation. Reports showed stable vital signs, no indication of hypotension, however, heart rate was 180 beats per minute.
70 mg amlodipine combined overdose with oxazepam of an unknown amount	Result of death in a 63-year-old woman.
105 mg amlodipine (intentional overdose)	Patient required hospitalisation, experiencing hypotension of 90/50 mmHg which stabilized after plasma expansion.
120 mg amlodipine (intentional overdose)	Patient required hospitalisation, gastric lavage and stayed normotensive.
140 mg amlodipine combined overdose with 10 x mefenamic acid capsules	Result of death in a 15-year-old girl.
250 mg amlodipine (intentional overdose)	Patient was asymptomatic and did not require hospital treatment.

Recommended treatment

In the event of a substantial overdose, establish active cardiac and respiratory monitoring. It is imperative that the patient's blood pressure is evaluated frequently.

In the event of hypotension, commence cardiovascular support (including extremities raised), and careful administration of fluids. If these methods do not alleviate the hypotension, vasopressor administration (for example, phenylephrine) should be contemplated with particular care taken to output of urine and circulating volume.

Amlodipine absorption can be reduced significantly with the use of activated charcoal immediately following the ingestion of amlodipine or in the two hours following. This has been reported in studies on healthy individuals after being administered amlodipine 10 mg. Attention should be given to having activated charcoal administered through a nasogastric tube (when the airway is protected) in patients that have a compromised gag reflex or are not completely conscious. Due to the possibility of haemodynamic instability and CNS depression developing quickly, ipecac-emesis is not advocated.

In the event of calcium channel blockade, intravenous calcium gluconate may assist in withdrawing the effects.

As amlodipine binds substantially to proteins, dialysis is not recommended.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

Amlodipine is a calcium ion influx inhibitor, also known as a calcium ion antagonist or slow channel blocker and works by preventing calcium ions moving through the transmembrane into the smooth and cardiac muscle.

The antihypertensive mechanism action of amlodipine on the vascular smooth muscle is a complete relaxant effect.

The exact process in which amlodipine alleviates angina is not completely understood but it is known that amlodipine decreases the total ischaemic burden by dilating the peripheral arterioles and therefore decreases the entire peripheral resistance or afterload in which the heart functions against. As the heart rate continues to be steady, the unburdening of the heart therefore decreases the requirements of oxygen and myocardial energy expenditure.

The amlodipine mechanism of action also most likely encompasses the dilatation of the main coronary arterioles and arteries (in both the ischaemic and normal areas). This dilatation reduces coronary vasoconstriction that is induced by smoking and increases the transfer of myocardial oxygen in individuals with coronary artery spasm (Prinzmetal's or variant angina).

During a 24-hour period, clinically significant blood pressure decreases are observed in both the standing and lying down positions in individuals with hypertension and who were given amlodipine dosing once per day.

Acute hypotension is not a concern because of the gradual onset of amlodipine action following administration.

For patients with angina, amlodipine administration once per day reduces both the frequency of angina attacks and nitroglycerine consumption. It also increases the onset time of angina, the time of total exercise and the period of time to 1 mm ST segment depression.

Use in Individuals with Heart Failure
Haemodynamic clinical studies and a controlled exercise centered clinical trial in heart failure (NYHA Class II-IV) individuals concluded that amlodipine does not result in clinical deterioration as evaluated by left ventricular ejection fraction, tolerance of exercise, and clinical symptomatology.

A placebo-controlled clinical study (PRAISE) that originated to assess individuals with heart failure (NYHA Class III-IV) and who were receiving angiotensin converting enzyme (ACE) inhibitors, digoxin and diuretics reported that amlodipine does not cause heightened risk mortality or mortality combined and does not lead to morbidity in individuals with heart failure.

In a follow-up placebo-controlled, long-term clinical study (PRAISE-2) in patients with heart failure (NYHA III and IV), who were not showing any clinical symptoms or results suggesting underlying ischaemic disease, and were on unchanged doses of ACE inhibitors, diuretics and digitalis, amlodipine showed it had no effect on the total cardiovascular mortality. Furthermore, amlodipine was also connected with an increase of pulmonary oedema reports, regardless of no significant change in worsening heart failure incidence compared to placebo in the same population (Please refer to Section 4.4 Special Warnings and Precautions of Use).

Amlodipine is regarded appropriate for the use in individuals who have asthma, gout or diabetes as it has not been associated with any plasma lipid changes or any adverse metabolic effects.

5.2 Pharmacokinetic properties

Absorption
When taken orally, amlodipine is absorbed well. Blood levels peak post administration between six to twelve hours. The mean absolute bioavailability following an individual therapeutic dose administered orally is 64% with a range between 52% and 88%. The distribution volume is about 20 L/kg. Amlodipine absorption following food consumption is not affected.

97.5% of amlodipine binds to plasma proteins when circulating, shown by *in vitro* studies.

Metabolism and Elimination
For amlodipine taken once per day, the terminal elimination half-life for plasma is approximately 35 to 50 hours. Following successive dosing over a period of seven to eight days, steady state plasma levels are attained.

The metabolism of amlodipine to its inactive metabolites occurs significantly in the liver where 60% of the metabolites and 10% of amlodipine that is unchanged are eliminated through the urine.

Amlodipine is not suitable for dialysis.

5.3 Preclinical safety data

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days (at a dose comparable with the human dose based on mg/kg), decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose given for mice in this study was close to the recommended clinical dose of 10 mg on a mg/m^2 basis and the highest dose given for rats was twice this amount*. For mice, this was close to the maximum tolerated dose (but not for rats).

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, dibasic calcium phosphate, sodium starch glycollate, magnesium stearate, and colloidal anhydrous silica.

6.2 Incompatibilities

None known.

6.3 Shelf life

2.5 mg tablets: Bottle, HDPE - 30 or 90 tablets – 24 months
2.5 mg, 5 mg and 10 mg tablets: Bottle, HDPE - 1000 tablets - 36 months.
5 mg and 10 mg tablets: PVC/Al/VMCH blister packs of 30 or 100 tablets – 24 months.
5 mg and 10 mg tablets: Bottle, HDPE - 90 tablets – 36 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

- 2.5 mg tablets: 30 or 90 tablets - Bottle, HDPE with Tekni-Plex Foil Liner Bottle with CRC Cap and Induction Liner.
- 2.5 mg tablets: 1000 tablets - Bottle, HDPE with non-CRC cap and silica gel bag.
- 5 mg tablets: 30 or 100 tablets - PVC/Al/VMCH blister packs.
- 5 mg tablets: 90 tablets - Bottle, HDPE with Tekni-Plex Foil Liner Bottle with CRC Cap and Induction Liner.
- 5 mg tablets: 1000 tablets - Bottle, HDPE with non-CRC cap and silica gel bag.
- 10 mg tablets: 30 or 100 tablets - PVC/Al/VMCH blister packs.
- 10 mg tablets: 90 tablets - Bottle, HDPE with Tekni-Plex Foil Liner Bottle with CRC Cap and Induction Liner.
- 10 mg tablets: 1000 tablets - Bottle, HDPE with non-CRC cap and silica gel bag.

Not all presentations are available.

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

2.5 mg tablets 26 May 2016
5 mg and 10 mg tablets 15 April 2010

10 DATE OF REVISION OF THE TEXT

10 June 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Reporting of suspected adverse reactions: updated the reporting URL as per Medsafe template
4.9	Information added on non-cardiogenic pulmonary oedema (NCPE). Added risk assessment wording as per Medsafe template