AUSTRALIAN PRODUCT INFORMATION –

AMLODIPINE/VALSARTAN NOVARTIS® 5/80
(amlodipine /valsartan) film-coated tablet
AMLODIPINE/VALSARTAN NOVARTIS® 5/160
(amlodipine /valsartan) film-coated tablet
AMLODIPINE/VALSARTAN NOVARTIS® 10/160
(amlodipine /valsartan) film-coated tablet
AMLODIPINE/VALSARTAN NOVARTIS® 5/320
(amlodipine /valsartan) film-coated tablet
AMLODIPINE/VALSARTAN NOVARTIS® 10/320
(amlodipine /valsartan) film-coated tablet

1 NAME OF THE MEDICINE

Amlodipine/valsartan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLODIPINE/VALSARTAN NOVARTIS 5/80, AMLODIPINE/VALSARTAN NOVARTIS 5/160, AMLODIPINE/VALSARTAN NOVARTIS 10/160, AMLODIPINE/VALSARTAN NOVARTIS 5/320 and AMLODIPINE/VALSARTAN NOVARTIS 10/320 are available as film-coated tablets in five strengths containing amlodipine (5 or 10 mg) and valsartan (80, 160 mg or 320mg) as: 5/80 mg, 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

AMLODIPINE/VALSARTAN NOVARTIS 5/80 (5 mg amlodipine and 80 mg valsartan): Dark yellow, round film-coated tablet with bevelled edge, debossed with NVR on one side and NV on the other.

AMLODIPINE/VALSARTAN NOVARTIS 5/160 (5 mg amlodipine and 160 mg valsartan): Dark yellow, ovaloid film-coated tablet with bevelled edge, debossed with NVR on one side and ECE on the other.

AMLODIPINE/VALSARTAN NOVARTIS 10/160 (10 mg amlodipine and 160 mg valsartan): Light yellow, ovaloid film-coated tablet with bevelled edge, debossed with NVR on one side and UIC on the other.

AMLODIPINE/VALSARTAN NOVARTIS 5/320 (5 mg amlodipine and 320 mg valsartan): Very dark yellow, ovaloid film-coated tablet with bevelled edge, debossed with NVR on one side and CSF on the other.

AMLODIPINE/VALSARTAN NOVARTIS 10/320 (10 mg amlodipine and 320 mg valsartan): Dark yellow, ovaloid film-coated tablet with bevelled edge, debossed with NVR on one side and LUF on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AMLODIPINE/VALSARTAN NOVARTIS is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose is one tablet per day of either AMLODIPINE/VALSARTAN NOVARTIS 5/80, 5/160, 10/160, 5/320 or 10/320. Both amlodipine and valsartan monotherapy can be taken with or without food. AMLODIPINE/VALSARTAN NOVARTIS should be consistently taken with or without food. It is recommended to take AMLODIPINE/VALSARTAN NOVARTIS with some water.

For convenience, patients adequately controlled on valsartan and amlodipine may be switched to AMLODIPINE/VALSARTAN NOVARTIS containing the same component doses from separate tablets. A patient whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy may be switched to combination therapy with AMLODIPINE/VALSARTAN NOVARTIS 5/80, 5/160, 10/160, 5/320 and 10/320. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

The elderly

Caution is advised when increasing the dose in elderly patients (see Section 5.2 Pharmacokinetic properties).

Children and adolescents

AMLODIPINE/VALSARTAN NOVARTIS is not recommended for use in patients aged below 18 years due to a lack of safety and efficacy data.

Patients with renal and hepatic impairment

No dosage adjustment is required for patients with mild to moderate renal impairment but caution should be exercised when administering AMLODIPINE/VALSARTAN NOVARTIS to patients with hepatic impairment or biliary obstructive disorders (see Section 4.4 Special warnings and precautions for use). Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Liver function should be monitored in patients with mild to moderate hepatic impairment .The daily dose of AMLODIPINE/VALSARTAN NOVARTIS should not exceed 5/80 mg in patients with mild to moderate hepatic impairment without cholestasis. AMLODIPINE/VALSARTAN NOVARTIS is contraindicated in severe hepatic and renal impairment and patients undergoing dialysis.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances, dihydropyridine derivatives, or to any of the excipients;
- Severe hepatic impairment; biliary cirrhosis and cholestasis;
- Severe renal impairment (GFR<30 ml/min/1.73 m^2) and patients undergoing dialysis;
- Pregnancy
- Concomitant use with aliskiren in patients with Type 2 diabetes mellitus (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension, Sodium and/or Volume Depleted Patients

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with AMLODIPINE/VALSARTAN NOVARTIS in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of AMLODIPINE/VALSARTAN NOVARTIS or close medical supervision at the start of treatment is recommended.

If hypotension occurs with AMLODIPINE/VALSARTAN NOVARTIS, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Increased Angina and/or Acute Myocardial Infarction

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina and/or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

Beta-blocker Withdrawal

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Renal Artery Stenosis

AMLODIPINE/VALSARTAN NOVARTIS should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney. Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Kidney Transplantation

To date there is no experience of the safe use of AMLODIPINE/VALSARTAN NOVARTIS in patients who have had a recent kidney transplantation.

Aortic and Mitral Valve Stenosis, Hypertrophic Obstructive Cardiomyopathy

As with all other vasodilators, special caution is indicated when using VASLARTAN/ AMLODIPINE NOVARTIS in patients with haemodynamically relevant aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Concomitant Use with ACE Inhibitors

Concomitant use of an angiotensin II receptor blocker and an ACE inhibitor may increase the risk of hyperkalaemia, renal failure, hypotension and syncope.

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. AMLODIPINE/VALSARTAN NOVARTIS should be immediately discontinued in patients who develop angioedema, and AMLODIPINE/VALSARTAN NOVARTIS should not be re-administered.

Dual blockade of the Renin-Angiotensin System (RAS)

Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in Patients with Heart Failure/Post-myocardial Infarction

In general, calcium channel blockers should be used with caution in patients with heart failure. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

Use of valsartan in patients with heart failure or post-myocardial infarction commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed. Patients with more complicated post-myocardial infarction courses may be at increased risk for hypotension and/or renal dysfunction. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. An assessment of renal function should always be conducted in patients with heart failure or post-myocardial infarction.

An increase in the mortality rate among patients who received a combination of valsartan, ACE inhibitors and beta blockers has been observed in clinical trials. Concurrent administration of ACE inhibitors, beta blockers and valsartan is not recommended.

Hepatic Injury

Cases of clinically significant liver disease have occurred with some angiotensin II receptor antagonists. Hepatitis has been reported rarely with valsartan.

Primary Hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through the renin-angiotensin-aldosterone system therefore use of AMLODIPINE/VALSARTAN NOVARTIS in these patients is not recommended.

Use in hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. In patients with mild to moderate hepatic impairment without cholestasis, AMLODIPINE/VALSARTAN NOVARTIS should be used with caution (see Section

5.2 Pharmacokinetic properties - Impaired hepatic function) and careful monitoring of liver function tests should be performed. The daily dose of AMLODIPINE/VALSARTAN NOVARTIS should not exceed 5/80 mg. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take AMLODIPINE/VALSARTAN NOVARTIS (see Section 4.3 Contraindications).

Use in renal impairment

No dosage adjustment of AMLODIPINE/VALSARTAN NOVARTIS is required for patients with mild to moderate renal impairment. Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Patients with severe renal impairment should not take AMLODIPINE/VALSARTAN NOVARTIS (see Section 4.3 Contraindications).

Use in the elderly

See Sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties

Paediatric use

The safety and efficacy of AMLODIPINE/VALSARTAN NOVARTIS in children and adolescents (below the age of 18 years) have not been established.

Effects on laboratory tests

Hyperkalaemia

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been conducted with AMLODIPINE/VALSARTAN NOVARTIS and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below.

Other antihypertensive agents:

Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Amlodipine

Simvastatin: Co-administration of simvastatin with multiple doses of amlodipine increases exposure to simvastatin compared to when simvastatin is administered alone. It is recommended that the dose of simvastatin be reduced to an appropriate dose in accordance with the Product Information of simvastatin for patients concomitantly on amlodipine.

CYP3A4 inhibitors: A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, hypericum perforatum [St John's Wort]): Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycaemic drugs.

Cyclosporin: The pharmacokinetics of cyclosporin were not altered when cyclosporin was coadministered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.

Grapefruit juice: Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Sildenafil: A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Dantrolene (infusion):Due to risk of hyperkalaemia, it is recommended that the concomitant administration of calcium channel blockers such as amlodipine with intravenous dantrolene be avoided in patients susceptible to malignant hyperthermia, and in the management of malignant hyperthermia.

Valsartan

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with AMLODIPINE/VALSARTAN NOVARTIS.

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Hepatic Transporters: Co-administration with inhibitors of the hepatic uptake transporter OATP1B1 (such as rifampicin, cyclosporin) or hepatic efflux transporter MRP2 (e.g. ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the renin-angiotensin system (RAS) with ARBs, ACEIs or aliskiren:

The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal

function compared to therapy with one RAS blocker. It is recommended to monitor blood pressure, renal function and electrolytes in patients on AMLODIPINE/VALSARTAN NOVARTIS and other agents that affect the RAS (see Section 4.4 Special warnings and precautions for use).

The concomitant use of ARBs including valsartan, or ACEIs, with aliskiren is contraindicated in patients with Type 2 diabetes mellitus (see Section 4.3 Contraindications).

Combination use of ACE inhibitors or angiotensin receptor antagonist, thiazide diuretics and anti-inflammatory drugs (NSAIDs or COX-2 inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, the use of an ACE inhibiting drug (ACE-inhibitors) or angiotensin receptor antagonist, a thiazide diuretic (including hydrochlorothiazide) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) at the same time increases the risk of renal impairment. Concomitant use of angiotensin II antagonists and NSAIDs in patients who are elderly, volume-depleted (including those on diuretic therapy) or have compromised renal function may lead to an increased risk of worsening renal function, including possible acute renal failure. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly when initiating or modifying treatment.

In monotherapy with valsartan: no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, frusemide, digoxin, atenolol, indomethacin hydrochlorothiazide, amlodipine, glibenclamide.

As valsartan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, frusemide, and warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific fertility studies were conducted with AMLODIPINE/VALSARTAN combination; however, testes, ovaries and secondary sex organs were evaluated in other toxicity studies with this combination. The primary and secondary sex organs were not affected in these toxicity studies, in which rats and marmosets were treated with this combination for up to 13 weeks.

Valsartan: Fertility of male and female rats was not affected at oral doses up to 200 mg/kg/day, with systemic exposure similar to that in human patients at the maximum recommended dose.

Amlodipine: 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 but in one rat study, adverse effects were found on male fertility.

Use in pregnancy – Pregnancy Category D

AMLODIPINE/VALSARTAN NOVARTIS must not be used during pregnancy (see Section 4.3 Contraindications) or in women planning to become pregnant. Healthcare professionals

prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, AMLODIPINE/VALSARTAN NOVARTIS must be discontinued as soon as possible.

Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause foetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS).

Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. The use of drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan. Pregnant women who are taking angiotensin II receptor antagonists (ARAs) should be changed as quickly as possible to other antihypertensive medication to maintain normal blood pressure. It is generally advisable not to use ARAs for the management of hypertension in women who are likely to become pregnant.

Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

In the event that neonates are exposed to AMLODIPINE/VALSARTAN NOVARTIS *in utero* and oliguria or hypotension occurs, direct attention towards support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

There was no evidence of teratogenicity in rats dosed with the amlodipine/valsartan combinations during organogenesis at doses up to 20:320 mg/kg/day PO. Foetotoxicity was observed in association with maternal toxicity (≥10:160 mg/kg/day) in rats at amlodipine/valsartan doses of 20:320 mg/kg/day and included decreased fetal weights, dilated ureters and delayed/incomplete ossification. The (AUC) exposures at these doses were 3-10x the expected human exposure to amlodipine/valsartan at the maximum proposed clinical dose (10:160mg/day).

No teratogenic effects were observed when valsartan alone was administered orally to mice and rats at a dose of 600 mg/kg/day and to rabbits at a dose of 10 mg/kg/day during the period of organogenesis. However, foetal losses were observed at the highest dose level in rabbits, and foetal weight was reduced at 600 mg/kg/day in rats and at 5 mg/kg/day in rabbits.

Administration of 600 mg/kg/day valsartan to rats prior to parturition and during lactation caused a decrease in birth weight, a reduction in post-natal growth and survival, and a slight delay in physical development of the offspring. A reduction of red blood cell parameters and evidence of changes in renal haemodynamics were observed at 200-600 mg/kg/day.

No teratogenic effects were found when 18 mg/kg/day amlodipine (base) was administered in rats or 10 mg/kg/day in rabbits. Amlodipine (7mg/kg/day as base) administered orally to

rats at or near parturition induced a prolongation of gestation time, an increase in number of stillbirths and decreased post-natal survival.

Use in lactation

It is not known whether valsartan and/or amlodipine are excreted in human milk. There are no studies with the amlodipine besylate/valsartan combination in lactating animals. Valsartan was excreted in the milk of lactating rats. A peri/postnatal study in rats with valsartan showed reductions in postnatal growth and survival, and a slight delay in physical development of the offspring when valsartan was administered to rats prior to parturition and during lactation at 600 mg/kg/day. No effects were observed at 200 mg/kg/day. It is therefore not advisable for women who are breast-feeding to use AMLODIPINE/VALSARTAN NOVARTIS.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Adverse Reactions with Suspected Relationship to AMLODIPINE/VALSARTAN NOVARTIS

The safety of AMLODIPINE/VALSARTAN NOVARTIS has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received amlodipine in combination with valsartan.

Adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Metabolism and nutrition disorders	
Uncommon:	Anorexia, hypercalcaemia, hyperlipidaemia, hyperuricaemia, hypokalaemia, hyponatraemia
Eye disorders	
Rare	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety

Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia, coordination abnormal
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhoea, nausea, abdominal pain, constipation, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness
Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	
Common:	oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush

Additional Information on the Combination

Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	N.A	N.A	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

An orthostatic blood pressure change, defined as a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moved from a sitting position to a standing position, was observed in 9.5% of patients receiving amlodipine/valsartan 5/320 mg, 8.7% receiving amlodipine/valsartan 10/320 mg compared to 7.4% receiving placebo.

Laboratory Evaluation

Very few hypertensive patients treated with amlodipine/valsartan showed notable changes in laboratory test results from baseline. There was a slightly higher incidence of notably increased blood urea nitrogen in the amlodipine/valsartan (5.5 %) and valsartan monotherapy (5.5%) groups as compared to the placebo group (4.7%).

In controlled trials, the incidence of notable laboratory changes with amlodipine/valsartan 10/320 mg, 5/320 mg and placebo were as follows: BUN (> 50% increase): 5.0%, 1.6%, and 4.7%, respectively; potassium (>20% increase): 2.0%, 3.3%, and 3.4%; ALT (>150% increase): 2.0%, 0.0%, and 0.9%; creatinine (>50% increase): 0.5%, 0.0%, and 0.6%; CK (>300% increase): 1.0%, 0.0%, and 0.9%. In a long term, open label, uncontrolled clinical trial of 5/320mg, increases in BUN greater than 50% were observed in 10.9% of the patients treated, increases in serum potassium greater than 20% were observed in 9.4% of the patients treated, increases in ALT greater than 150% were observed in 2.8% of the patients treated, increases in creatinine greater than 50% were observed in 1.3% of the patients treated, and increases in CK greater than 300% were observed in 1% of the patients treated.

Additional Information on Individual Components

Adverse reactions previously reported with one of the individual components may occur with AMLODIPINE/VALSARTAN NOVARTIS even if not observed in clinical trials.

Amlodipine

Other additional adverse experiences reported in clinical trials and post marketing reports with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:

The most commonly observed adverse event was vomiting.

Less commonly observed adverse events were peripheral ischaemia, alopecia, anorexia, altered bowel habits, dyspepsia, dysphagia, flatulence, dyspnoea, epistaxis, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, malaise, sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, depersonalisation, mood changes, pain, rigors, weight gain, arthrosis, muscle cramps, myalgia, hypoesthesia, dysgeusia, tremor, peripheral neuropathy, pancreatitis, leucopenia, thrombocytopenia, purpura, vasculitis, conjunctivitis, diplopia, eye pain, photosensitivity, micturition frequency and disorder, nocturia, sweating increased, thirst, angioedema and erythema multiforme.

Rarely observed adverse events were cardiac failure, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, increased appetite, loose stools, coughing, dysuria, parosmia, taste perversion, xerophthalmia and weight decrease.

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

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (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.

Exceptional cases of extrapyramidal syndrome have been reported.

In a long-term placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic 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.

Risk of Myocardial Infarction or Increased Angina: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) has also been reported with calcium channel blocker therapy. These adverse events may not be distinguishable from the natural history of the underlying disease.

Valsartan

Other additional adverse experiences reported in clinical trials and post marketing reports with valsartan monotherapy in the hypertension indication, irrespective of their causal association with the study drug, were as follows:

Viral infections, upper respiratory infections, pharyngitis, sinusitis, rhinitis, neutropenia, thrombocytopenia, insomnia, libido decrease, myalgia, dyspepsia, flatulence, muscle cramps, chest pain, anorexia, vomiting, dyspnoea, elevated liver enzymes and very rare reports of hepatitis. Altered renal function (especially in patients treated with diuretics or in patients with renal impairment), acute renal failure, renal insufficiency, angioedema and hypersensitivity (vasculitis, serum sickness) can occur.

Laboratory Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of valsartan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking valsartan and 0.6% given placebo in controlled trials of hypertensive patients. In heart failure patients, increases in serum creatinine greater than 50% were observed in 3.9% of valsartan treated patients compared to 0.9% of placebo treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan plus captopril-treated patients, and 3.4% of captopril-treated patients.

Blood urea nitrogen: In heart failure trials, increases in blood urea nitrogen (BUN) greater than 50% were observed in 16.6% of patients treated with valsartan compared to 6.3% of patients treated with placebo.

Haematocrit and haemoglobin: Greater than 20% decreases in haemoglobin and haematocrit were observed in 0.4% and 0.8% respectively, of valsartan patients compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anaemia.

Liver function tests: Occasional elevations (greater than 150%) of liver function values were reported in patients treated with valsartan. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver function values. Elevated liver enzymes have also been reported in post-marketing surveillance.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Serum potassium: In patients with hypertension, increases in serum potassium greater than 20% were observed in 4.4% of patients treated with valsartan compared to 2.9% of placebo-treated patients. No patients treated with valsartan discontinued therapy for hyperkalaemia. In heart failure patients, increases in serum potassium greater than 20% were observed in 10.0% of valsartan treated patients compared to 5.1% of placebo treated patients.

Post-marketing Experience

Amlodipine

Gynaecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalisation, have been reported in association with use of amlodipine.

Valsartan

The following additional adverse reactions have been reported in post-marketing experience with valsartan:

- Blood and Lymphatic: There are very rare reports of thrombocytopenia.
- Hypersensitivity: There are rare reports of angioedema.
- Digestive*:* Elevated liver enzymes and very rare reports of hepatitis.
- Renal: Impaired renal function.
- Clinical Laboratory Tests: Hyperkalemia.
- Dermatologic: Alopecia.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers. Dermatitis bullous and hyponatraemia of unknown incidence have been reported.

4.9 OVERDOSE

Symptoms

There is no experience of overdose with AMLODIPINE/VALSARTAN NOVARTIS yet. Overdose with valsartan may result in pronounced hypotension with dizziness which could lead to depressed level of consciousness, circulatory collapse and/or shock. Overdose with amlodipine may result in excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonists. Hypotension and bradycardia are usually seen within one to five hours

following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to seven days. Marked and potentially 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.

Treatment

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to AMLODIPINE/VALSARTAN NOVARTIS overdose 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. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. If the ingestion is recent, induction of vomiting or gastric lavage may be considered. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: dihydropyridine derivatives (amlodipine) combinations with angiotensin II antagonists, plain (valsartan).

Mechanism of action

AMLODIPINE/VALSARTAN NOVARTIS combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II (Ang II) antagonist class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine: The amlodipine component of AMLODIPINE/VALSARTAN NOVARTIS inhibits the transmembrane entry 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, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not

accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans. Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Valsartan: Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The AT_2 receptor subtype has not been definitely shown to be associated with cardiovascular homeostasis. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has about a 20,000-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.4 % versus 7.9 %, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5 % of trial subjects receiving valsartan and 19.0 % of those receiving a thiazide diuretic experienced cough compared with 68.9 % of those treated with an ACE inhibitor ($P < 0.05$).

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours and the peak reduction in blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dose administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Clinical trials

Over 1,400 hypertensive patients received AMLODIPINE/VALSARTAN NOVARTIS once daily in 2 placebo-controlled trials. Over 1100 patients received AMLODIPINE/VALSARTAN NOVARTIS once daily in 2 active-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 mmHg and < 110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Study A2201 was a double-blind placebo-controlled dose-response study of 1911 patients with mild-to-moderate hypertension receiving combinations of amlodipine and valsartan (2.5/40, 2.5/80, 2.5/160, 2.5/320, 5/40, 5/80, 5/160, 5/320 mg), or amlodipine alone (2.5 or 5 mg), valsartan alone (40, 80, 160, or 320 mg) or placebo. At week 8 endpoint, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures (Tables 1 and 2), however the control rates varied (Table 3).

Table 1 Study A2201 Mean change in sitting diastolic blood pressure (mmHg) from baseline at Week 8 endpoint (Mean baseline diastolic BP was 99.3 mmHg)

Amlodipine	Valsartan				
	0 mg	40 mg	80 mg	160 mg	320 mg
0 mg	-6.4	-9.9	-9.5	-10.9	-13.2
2.5 mg	-9.1	-10.6	-13.1	-13.0	-13.91
5 mg	-11.1	-14.4	-14.2	-14.0	-15.7

Table 2 Study A2201 Mean change in sitting systolic blood pressure (mmHg) from baseline at Week 8 endpoint (Mean baseline systolic BP was 152.8 mmHg)

Amlodipine	Valsartan				
	0 mg	40 mg	80 mg	160 mg	320 mg
0 mg	-6.2	-11.9	-12.9	-14.3	-16.3
2.5 mg	-12.9	-15.3	-16.3	-16.2	-17.9
5 mg	-14.8	-19.6	-20.7	-19.4	-22.4

Table 3 Study A2201 Control Rates* (%) at Week 8 endpoint

Amlodipine	Valsartan				
	0 mg	40 mg	80 mg	160 mg	320 mg
0 mg	33.9	52.0 [p]	48.8 [p]	58.3 [p]	67.2 [p]
2.5 mg	50.0 [p]	46.9 [p]	67.4 [pva]	72.8 [pva]	68.0 [pa]
5 mg	64.8 [p]	70.7 [pv]	73.0 [pv]	70.1 [pv]	82.5 [pva]

*Control rate was defined as mean sitting diastolic blood pressure <90 mmHg

p = statistically significant vs placebo (p<0.05)

v = statistically significant vs valsartan (p<0.05)

a = statistically significant vs amlodipine (p<0.05)

Study A2307 was a double-blind, placebo-controlled dose-response study of 1250 patients with mild to moderate hypertension treated with two combinations of amlodipine and valsartan (10/160 and 10/320 mg), or amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. At week 8 endpoint, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures (Tables 4 and 5), however the control rates varied (Table 6).

Table 4 Study A2307 Mean change in sitting diastolic blood pressure (mmHg) from baseline at Week 8 endpoint (Mean baseline diastolic BP was 99.1 mmHg)

Amlodipine	Valsartan		
	0 mg	160 mg	320 mg
0 mg	-8.2	-12.8	-12.8
10 mg	-15.0	-17.2	-18.1

Table 5 Study A2307 Mean change in sitting systolic blood pressure (mmHg) from baseline at Week 8 endpoint (Mean baseline systolic BP was 156.7 mmHg)

Amlodipine	Valsartan		
	0 mg	160 mg	320 mg
0 mg	-11.0	-18.1	-18.5
10 mg	-22.2	-26.6	-26.9

Table 6 Study A2307 Control Rates* (%) at Week 8 endpoint

Amlodipine	Valsartan		
	0 mg	160 mg	320 mg
0 mg	42.6	70.5 [p]	63.8 [p]
10 mg	80.1 [p]	81.8 [pv]	84.1 [pv]

*Control rate was defined as mean sitting diastolic blood pressure <90 mmHg
p = statistically significant vs placebo ($p<0.05$)
v = statistically significant vs valsartan ($p<0.05$)
a = statistically significant vs amlodipine ($p<0.05$)

Study A2305 was a double-blind, active-controlled study of 947 patients with mild to moderate hypertension who were not adequately controlled on valsartan 160 mg. Patients received treatment of two combinations of amlodipine and valsartan (10/160 and 5/160 mg), or valsartan alone (160 mg). At week 8 endpoint, the combination treatments were statistically significantly superior to their monotherapy component in reduction of diastolic and systolic blood pressures.

Table 7 Study A2305 Mean change in sitting diastolic/systolic blood pressure (mmHg) from baseline and control rates* (%) at Week 8 endpoint (Mean baseline BP was 149.5/96.5 (systolic/diastolic) mmHg)

	Diastolic BP		Systolic BP		Control Rate (%)
	Mean change	Treatment difference	Mean change	Treatment difference	
AMLODIPINE/VALSARTAN NOVARTIS 10/160 mg	-11.4	-4.8	-13.9	-5.7	75.3
AMLODIPINE/VALSARTAN NOVARTIS 5/160 mg	-9.6	-3.1	-12.0	-3.9	62.4
valsartan 160 mg	-6.6	-	-8.2	-	52.6

* Control rate was defined as mean sitting diastolic blood pressure <90 mmHg

Study A2306 was a double-blind, active-controlled study of 944 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 10 mg. Patients received a combination of amlodipine and valsartan (10/160 mg), or amlodipine alone (10 mg). At week 8 endpoint, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Table 8 Study A2306 Mean change in sitting diastolic/systolic blood pressure (mmHg) from baseline and control rates* (%) at Week 8 endpoint (Mean baseline BP was 147.0/95.1 (systolic/diastolic) mmHg)

	Diastolic BP		Systolic BP		Control Rate (%)
	Mean change	Treatment difference	Mean change	Treatment difference	
AMLODIPINE/VALSARTAN NOVARTIS 10/160 mg	-11.8	-1.8	-12.7	-1.9	77.8
amlodipine 10 mg	-10.0		-10.8		66.5

* Control rate was defined as mean sitting diastolic blood pressure <90 mmHg

AMLODIPINE/VALSARTAN NOVARTIS was also studied in an active-controlled study of 130 hypertensive patients with diastolic blood pressure ≥110mmHg and <120mmHg. In this study (baseline blood pressure 171/113mmHg), an AMLODIPINE/VALSARTAN NOVARTIS regimen of 5mg/160mg titrated to 10mg/160mg reduced sitting blood pressure at Week 6 endpoint by 36/29mmHg as compared to 32/28mmHg with a regimen of lisinopril/hydrochlorothiazide 10mg/12.5mg titrated to 20mg/12.5mg (not available in Australia).

Two open-label one year extension studies (A2201E and A2307E) of the combination of amlodipine and valsartan were conducted in patients with mild to moderate hypertension recruited from Study 2201 and Study 2307, respectively. Patients needed to successfully complete the core studies with well controlled blood pressure and no serious drug-related adverse experiences. The results demonstrated that amlodipine/valsartan 160/5, 160/10 and 5/320 are effective in providing long-term blood pressure.

In patients whose blood pressure is adequately controlled with amlodipine but who experience unacceptable oedema, combination therapy may achieve similar blood pressure control with less oedema.

Age, gender and race did not influence the response to AMLODIPINE/VALSARTAN NOVARTIS.

No clinical outcomes studies have been conducted on cardiovascular morbidity and mortality with AMLODIPINE/VALSARTAN NOVARTIS.

There have been no studies conducted to evaluate as a primary endpoint the additional blood pressure lowering effects on the direct titration of patients from AMLODIPINE/VALSARTAN NOVARTIS 10/160 or below to the higher strengths of 5/320 or 10/320.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Valsartan: Peak plasma concentrations are reached 2 to 4 hours after dosing. The amount absorbed varies widely. Mean absolute bioavailability is 23% and the bioavailability relative to an oral solution is 59%.

The pharmacokinetics of valsartan are linear over the dose range 80 - 320 mg. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

When valsartan is given with food, the area under the plasma concentration-time curve (AUC) of valsartan is reduced by 48% although, from about 8 h post dosing, plasma valsartan concentrations are similar for the fed and fasted group.

Amlodipine/valsartan: Following oral administration of AMLODIPINE/VALSARTAN NOVARTIS peak plasma concentrations of amlodipine and valsartan are reached in 6-8 and 3 hours, respectively. The rate and extent of absorption of AMLODIPINE/VALSARTAN NOVARTIS are equivalent to the bioavailability of amlodipine and valsartan when administered as individual tablets.

Distribution

Amlodipine: Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Valsartan: Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L) indicating that valsartan does not distribute into tissues extensively.

Metabolism

Amlodipine: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Valsartan: Valsartan does not undergo extensive biotransformation. Only approximately 25% of absorbed drug is metabolised. The primary metabolite is valeryl 4-hydroxy valsartan, which is pharmacologically inactive. The enzyme(s) responsible for valsartan metabolism have not been identified.

Excretion

Amlodipine: Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan: Valsartan shows bi-exponential decay kinetics with a $t_{1/2}\alpha$ of about 1h and a $t_{1/2}\beta$ of about 9.5 hours. After oral dosing, 83% of the dose is excreted in the faeces and 13% in the urine, mainly as unchanged compound. Following intravenous administration, renal clearance of valsartan accounts for about 30% of total plasma clearance. Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 90 L/h).

Pharmacokinetics in children: No pharmacokinetic data are available in the paediatric population.

Pharmacokinetics in the elderly (aged 65 years or older): Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.

Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly compared to younger patients.

Pharmacokinetics in patients with impaired renal function: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, there is no apparent correlation between renal function (measured by creatinine clearance) and systemic exposure to valsartan (measured by AUC) in patients with different degrees of renal failure. A trial in 5 normotensive patients undergoing haemodialysis demonstrated that complete loss of renal function does not lead to a gross increase in the exposure to valsartan and does not have a major impact on the kinetics of valsartan. This study also confirmed that valsartan is not removed from the plasma by haemodialysis.

Pharmacokinetics in patients with impaired hepatic function: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur.

About 70% of the absorbed valsartan dose is excreted in the bile, mainly as unchanged compound. The AUC with valsartan has been observed to approximately double in patients with mild or moderate hepatic impairment including patients with biliary obstructive disorders (see Section 4.4 Special warnings and precautions for use- Use in hepatic impairment). There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see Section 4.3 Contraindications).

Care should be exercised in patients with liver disease (see Section 4.4 Special warnings and precautions for use).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with the amlodipine/valsartan combination.

Valsartan: Genotoxicity studies showed that valsartan does not cause gene mutation in bacterial or mammalian cells, nor does it induce chromosomal damage *in vitro* or *in vivo*.

Amlodipine did not induce gene mutation in bacteria or mouse lymphoma cells, and was not clastogenic in human lymphocytes, Chinese hamster V79 fibroblast cells (*in vitro*), or mouse bone marrow cells (*in vivo*).

Carcinogenicity

No carcinogenicity studies have been conducted with the amlodipine/valsartan combination.

Valsartan: In animal studies, there was no clear evidence of carcinogenic activity when valsartan was administered in the diet to male and female mice at doses up to 160 mg/kg/day for two years, but systemic exposure (plasma AUC value) at this dose level was lower than that achieved in humans. There was no clear evidence of carcinogenic activity in male or female rats at up to 200 mg/kg/day with plasma concentrations approximately 1.5 times the concentrations achieved in humans (based on AUC) at the maximum recommended dose (320 mg).

Amlodipine: The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, crospovidone, colloidal anhydrous silica,, magnesium stearate, hypromellose, titanium dioxide (except 5/320), iron oxide yellow, macrogol 4000, talc-purified, iron oxide red (10/160 and 5/320 only) and sodium starch glycollate (5/320 and 10/320 only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 degrees Celsius. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

AMLODIPINE/VALSARTAN NOVARTIS 5/80 (5 mg amlodipine and 80 mg valsartan): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN NOVARTIS 5/160 (5 mg amlodipine and 160 mg valsartan): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN NOVARTIS 10/160 (10 mg amlodipine and 160 mg valsartan): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN NOVARTIS 5/320 (5 mg amlodipine and 320 mg valsartan): PA/Al/PVC/Al or PVC/PE/PVDC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN NOVARTIS 10/320 (10 mg amlodipine and 320 mg valsartan): PA/Al/PVC/Al or PVC/PE/PVDC/Al blister packs of 7, 14, 28, 30 and 56.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

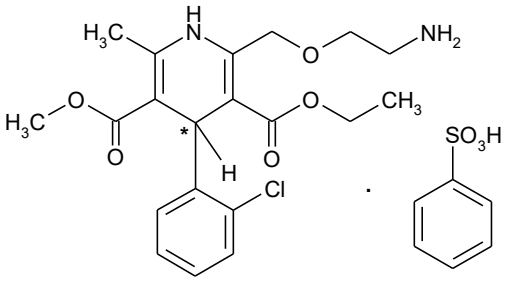
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

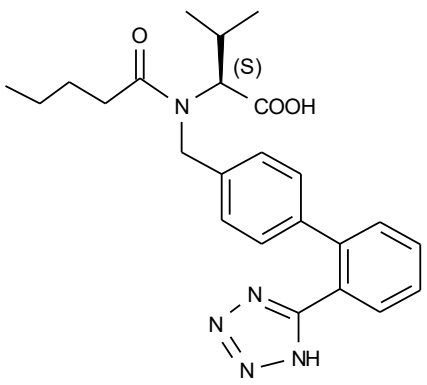
Active ingredients (INN): amlodipine besylate, valsartan

Amlodipine besylate is a white or almost white powder that is slightly soluble in water and sparingly soluble in ethanol. Valsartan is a white to practically white microcrystalline and slightly bitter tasting powder. It is soluble in ethanol and methanol and slightly soluble in water.

Chemical structure



and enantiomer



Amlodipine (as the besylate salt)

(3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate)

Valsartan

(N-Pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4ylmethyl]-L-valine)

CAS number: 111470-99-6

Molecular formula: $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$

Molecular weight: 567.06

CAS number : 137862-53-4

Molecular formula: $C_{24}H_{29}N_5O_3$

Molecular weight: 435.5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

Level 25, Victoria Cross Tower

155 Miller Street

North Sydney NSW 2060

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9 DATE OF FIRST APPROVAL

12 August 2008

10 DATE OF REVISION

16 June 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Update to container blister details
8	Sponsor address update

Internal document code: vaa160626i based on CDS 31-Oct-2013