AUSTRALIAN PRODUCT INFORMATION

AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/12.5®
(AMLODIPINE /VALSARTAN/HYDROCHLOROTHIAZIDE) FILM-COATED TABLET
AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/25®
(AMLODIPINE /VALSARTAN/HYDROCHLOROTHIAZIDE) FILM-COATED TABLET
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AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/12.5®
(AMLODIPINE /VALSARTAN/HYDROCHLOROTHIAZIDE) FILM-COATED TABLET
AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25®
(AMLODIPINE /VALSARTAN/HYDROCHLOROTHIAZIDE) FILM-COATED TABLET

1 NAME OF THE MEDICINE

Amlodipine /valsartan/hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/12.5®, AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/25®, AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/12.5®, AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/25®, and AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25® are available as film-coated tablets in five strengths containing amlodipine (5 or 10 mg), valsartan (160 or 320 mg) and hydrochlorothiazide (12.5 or 25 mg) as: 5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25mg and 10/320/25 mg.

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

3 PHARMACEUTICAL FORM

AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/12.5® (5 mg amlodipine, 160 mg valsartan and 12.5 mg hydrochlorothiazide): white, non-scored, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VCL” on the other.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/12.5® (10 mg amlodipine, 160 mg valsartan and 12.5 mg hydrochlorothiazide): pale yellow, non-scored, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VDL” on the other.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/25® (5 mg amlodipine, 160 mg valsartan and 25 mg hydrochlorothiazide): yellow, non-scored, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VEL” on the other.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/25® (10 mg amlodipine, 160 mg valsartan and 25 mg hydrochlorothiazide): brown-yellow, non-scored, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VHL” on the other.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25® (10 mg amlodipine, 320 mg valsartan and 25 mg hydrochlorothiazide): brown-yellow, non-scored, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VFL” on the other.

AMLODIPINE/VALSARTAN/HCT NOVARTIS tablets are non-divisible and cannot be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AMLODIPINE/VALSARTAN/HCT NOVARTIS is indicated ONLY as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual –component formulation with a single-component formulation, all components at the same dose level. Treatment should not be initiated with these fixed-dose combinations (see Section 4.2 Dose and method of administration).

4.2 DOSE AND METHOD OF ADMINISTRATION

AMLODIPINE/VALSARTAN/HCT NOVARTIS is ONLY indicated as substitution therapy for the treatment of hypertension in patients whose blood pressure is already adequately controlled on the triple combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single component formulations or as dual–component formulation with a single-component formulation, all components at the same dose level.

Therefore, if blood pressure is not controlled on one of the three possible dual combination therapies, then any third monotherapy must be first added as an individual therapy until dose titration is complete and BP control established before the triple fixed-dose combination may be introduced.

Similarily, there can be no direct dose-titration within the AMLODIPINE/VALSARTAN/HCT NOVARTIS product range. If a patient’s blood pressure is uncontrolled at one of the lower dosage of the combination, dose titration must be carried out with the separately administered components.

Children and adolescents

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

Patients with renal impairment

AMLODIPINE/VALSARTAN/HCT NOVARTIS is contraindicated in severe renal impairment (creatinine clearance < 30mL/min) (see Section 4.3 Contraindications). No dosage adjustment is required for patients with mild to moderate renal impairment (see Section 4.4 Special warnings and precautions

for use). Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment.

Patients with hepatic impairment

AMLODIPINE/VALSARTAN/HCT NOVARTIS is contraindicated in severe hepatic impairment, biliary cirrhosis or cholestasis and in patients undergoing dialysis (see Section 4.3 Contraindications). In patients with mild to moderate hepatic impairment without cholestasis the maximum recommended dose is 80 mg valsartan, and therefore, AMLODIPINE/VALSARTAN/HCT NOVARTIS is not suitable in this group of patients (see Section 4.4 Special warnings and precautions for use).

Heart failure and coronary artery disease

There is limited experience with the use of AMLODIPINE/VALSARTAN/HCT NOVARTIS, particularly at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25.

Elderly (age 65years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25, since available data in this patient population are limited.

Administration

The recommended dose is one tablet per day. AMLODIPINE/VALSARTAN/HCT NOVARTIS can be taken with or without food. It is recommended to take AMLODIPINE/VALSARTAN/HCT NOVARTIS with some water.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances, dihydropyridine derivatives, other sulfonamide-derived drugs, or to any of the excipients
- Severe hepatic impairment; biliary cirrhosis and cholestasis
- Severe renal impairment (GFR<30 ml/min/1.73 m^2), anuria and patients undergoing dialysis
- Refractory hypokalaemia, hyponatremia, hypercalcemia and symptomatic hyperuricemia
- 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, including orthostatic hypotension was seen in 1.7% of patients treated with the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS (10/320/25 mg) compared to 1.8% of valsartan/hydrochlorothiazide (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of hydrochlorothiazide/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-

angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of AMLODIPINE/VALSARTAN/HCT NOVARTIS, or the treatment should start under close medical supervision.

If excessive hypotension occurs with AMLODIPINE/VALSARTAN/HCT 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.

Renal Artery Stenosis

AMLODIPINE/VALSARTAN/HCT 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/HCT 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 AMLODIPINE/VALSARTAN/HCT NOVARTIS in patients with haemodynamically relevant aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

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/HCT NOVARTIS should be immediately discontinued in patients who develop angioedema, and AMLODIPINE/VALSARTAN/HCT 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.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Association Classification) III and IV heart failure of non-ischaemic 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.

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25 mg, since available data in these patient populations is limited (see Section 4.4 Special warnings and precautions for use - Increased Angina and/or Acute Myocardial Infarction).

Systemic Lupus Erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

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/ HCT Novartis in these patients is not recommended.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with AMLODIPINE/VALSARTAN/HCT NOVARTIS, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. The risk for non-melanoma skin cancer appears to increase with long-term use (see section 5.1 Pharmacodynamic Properties). Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism fornon-melanoma skin cancer..

Patients taking hydrochlorothiazide should be informed of the risk of non-melanoma skin cancer and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined, potentially including histological examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced non-melanoma skin cancer (see section 4.8 Adverse effects (undesirable effects)).

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, AMLODIPINE/VALSARTAN/HCT NOVARTIS should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Use in hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan, and therefore, AMLODIPINE/VALSARTAN/HCT NOVARTIS is not suitable in this group of patients. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take AMLODIPINE/VALSARTAN/HCT NOVARTIS (see Section 4.3 Contraindications).

Thiazides, like other diuretics, may precipitate electrolyte imbalance, hepatic encephalopathy and hepato-renal syndrome when used to treat cirrhotic ascites.

Use in renal impairment

No dosage adjustment of AMLODIPINE/VALSARTAN/HCT NOVARTIS is required for patients with mild to moderate renal impairment. Renal function has a marked effect on the kinetics of hydrochlorothiazide (see Section 5.2 Pharmacokinetic properties – Renal Impairment). Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. AMLODIPINE/VALSARTAN/HCT NOVARTIS should be used with caution and monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Patients with severe renal impairment should not take AMLODIPINE/VALSARTAN/HCT NOVARTIS (see Section 4.3 Contraindications).

Use in the elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25 mg, since available data in this patient population are limited.

Paediatric use

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

Effects on laboratory tests

Serum Electrolyte Changes

Amlodipine/valsartan/hydrochlorothiazide: In the controlled trial of AMLODIPINE/VALSARTAN/HCT NOVARTIS, the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.

In the controlled trial of AMLODIPINE/VALSARTAN/HCT NOVARTIS in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium <3.5 mEq/L) at any time post-baseline with the maximum dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS (10/320/25 mg) was 9.9% compared to 24.5% with hydrochlorothiazide/amlodipine (25/10 mg), 6.6% with valsartan/hydrochlorothiazide (320/25 mg), and 2.7% with amlodipine/valsartan (10/320 mg). One

patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the AMLODIPINE/VALSARTAN/HCT NOVARTIS and hydrochlorothiazide/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with AMLODIPINE/VALSARTAN/HCT NOVARTIS compared to 0.2-0.7% with the dual therapies.

Hydrochlorothiazide: Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution.

Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide. Frequent monitoring of potassium is recommended. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), AMLODIPINE/VALSARTAN/HCT NOVARTIS should be discontinued. Correction of hypokalaemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatremia and hypochloraemic alkalosis. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals.

Other Metabolic Disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Hyperuricaemia may occur or gout may be precipitated in certain patients receiving thiazide therapy. Thiazides may reduce urinary calcium excretion and cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Pathological changes in the parathyroid gland of patients with hypercalcaemia and hypophosphataemia have been observed in a few patients on prolonged thiazide therapy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal interaction studies with other medicinal products were performed with AMLODIPINE/VALSARTAN/HCT NOVARTIS. Thus, only information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

However, it is important to take into account that AMLODIPINE/VALSARTAN/HCT NOVARTIS may increase the antihypertensive effect of other antihypertensive agents (e.g. alpha blockers, other

diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia).

Concomitant use not recommended:

Valsartan/ Amlodipine/ HCT Novartis individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Amlodipine	*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.
	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.

Caution required with concomitant use:

Valsartan/ Amlodipine/ HCT Novartis individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
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)	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 & oral hypoglycaemic drugs.
Valsartan	*Inhibitors of hepatic uptake transporter OATP1B1 (e.g. rifampicin, cyclosporin) and efflux transporter MRP2 (e.g. ritonavir)*	Systemic exposure to valsartan may be increased.
	Medicinal products affecting 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.
	Dual blockade of the renin-angiotensin system (RAS) with ARBs, ACEIs or aliskiren	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/HCT NOVARTIS and other agents that affect the RAS (see Section 4.4 Special warnings and precautions for use)

Valsartan and HCT	*Lithium*	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with AMLODIPINE/VALSARTAN/HCT NOVARTIS. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.
	Medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics)	Periodic monitoring of serum potassium and ECG is recommended when AMLODIPINE/VALSARTAN/HCT NOVARTIS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes. • Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide) • Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide) • Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, suitopride, amisulpride, tiapride, pimozide, haloperidol, droperidol, methadone) • Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, moxifloxacine, terfenadine, vincamine i.v.) Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances. See Section 4.4 Special warnings and precautions for use, Effects on laboratory tests, Serum Electrolyte Changes
	Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid	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

	(>3g/day), indomethacin and non-selective NSAIDs	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.
HCT	*Alcohol, anesthetics and sedatives*	Potentiation of orthostatic hypotension may occur with concomitant administration of thiazides with alcohol, barbiturates or narcotics.
	Amantadine	Thiazides, including hydrochlorothiazide may increase the risk of adverse reactions caused by amantadine.
	Anticholinergic agents (e.g. atropine, biperiden, cisapride)	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.
	Antidiabetic agents (e.g. insulin and oral antidiabetic agents e.g. Metformin)	Thiazide diuretics, including hydrochlorothiazide, may increase blood glucose. It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
	Diazoxide	Thiazide diuretics, including hydrochlorothiazide may enhance the hyperglycaemic effect of diazoxide.
	Carbamazepine	Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.
	Cholestyramine and cholestipol resins	Single doses of cholestyramine or colestipol resins reduced the absorption of hydrochlorothiazide by up to 85 and 43 percent respectively. Staggering the administration of hydrochlorothiazide and resin should be considered to minimize the interaction.
	Cyclosporin	Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)	Co-administration of thiazide diuretics, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
Digitalis glycosides	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.
Iodine contrasting agents	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
Medicinal product affecting Potassium (kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics)	The hypokalaemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, adrenocorticotropic hormone, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhytmics. If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (See Section 4.4 Special warnings and precautions for use, Effects on laboratory test, Serum electrolyte changes**)**.
Medicinal product affecting Sodium (antidepressants, antipsychotics, antiepileptics)	The hyponatremic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long term administration of these drugs.
Medicinal products used in the treatments for gout (probenecid, sulfinpyrazone and allopurinol)	Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol. Thiazides may also increase serum uric acid levels, and the dose of uricosuric agents such as probenecid or sulfinpyrazone may need to be increased.
Methyldopa	There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants (e.g. curare derivatives).
Other diuretics and antihypertensive agents (e.g.guanethidine, methyldopa, beta-	The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs. The thiazide component of AMLODIPINE/VALSARTAN/HCT

	blockers,vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors)	NOVARTIS may enhance the hyperglycaemic effect of beta-blockers.
	Pressor amines(e.g. noradrenalin, adrenaline)	The effect of pressor amines may be decreased.
	Tetracyclines	Concomitant administration of tetracyclines and thiazide diuretics increases the risk for tetracycline induced increase in urea. This interaction is probably not applicable to doxycycline.
	Vitamin D and Calcium salts	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

No interactions:

Valsartan/ Amlodipine/ HCT Novartis individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Valsartan	*Highly protein-bound, such as diclofenac, frusemide and warfarin*	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. Some of these substances could interact with the hydrochlorothiazide component of Valsartan/ Amlodipine/HCT Novartis (See Section 4.5 Interactions with other medicines and other forms of interactions, Caution required with concomitant use – HCT).
	Others (cimetidine, warfarin, frusemide, digoxin, atenolol, indomethacin hydrochlorothiazide, amlodipine, glibenclamide)	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. Some of these substances could interact with the hydrochlorothiazide component of Valsartan/ Amlodipine/HCT Novartis (See Section 4.5 Interactions with other medicines and other forms of interactions, Caution required with concomitant use – HCT).

Amlodipine	*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.
	Cyclosporin	The pharmacokinetics of cyclosporin were not altered when cyclosporin was coadministered with amlodipine in renal transplant patients. The patients were not taking corticosteroids. (See Section 4.5 Interactions with other medicines and other forms of interactions, Caution required with concomitant use, HCT – *Cyclosporin*).
	Others	In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, antacids (containing aluminium hydroxide gel, magnesium hydroxide and simethicone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific fertility studies were conducted with the amlodipine/valsartan/hydrochlorothiazide combination.

Testes, ovaries and secondary sex organs were evaluated in other toxicity studies with the amlodipine/valsartan 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.

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.

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.

Hydrochlorothiazide: The effects of valsartan and hydrochlorothiazide in combination and hydrochlorothiazide alone on fertility have not been investigated.

Use in pregnancy – Pregnancy Category D

AMLODIPINE/VALSARTAN/HCT 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/HCT 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 foetal 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. In case of accidental exposure to ARB therapy, appropriate foetal monitoring should be considered. Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

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/HCT 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.

No reproductive toxicity studies have been conducted with amlodipine, valsartan and hydrochlorothiazide combination. 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 foetal 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).

There was no evidence of teratogenicity in mice, rats and rabbits dosed with the valsartan/hydrochlorothiazide combination during organogenesis at up to 600/187.5, 200/62.5 and 10/3.125 mg/kg/day PO, respectively. Foetotoxicity was observed in association with maternal

toxicity in rats and rabbits at valsartan/hydrochlorothiazide doses of 200/62.5 mg/kg/day and 10/3.125 mg/kg/day. Decreased foetal weights, absent renal papillae and delayed ossification were observed in rats and increased late resorptions in rabbits.

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.

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Use in lactation

It is not known whether valsartan is excreted in human milk. It is reported that amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide crosses the placenta and is excreted in human milk. It is therefore not advisable for women who are breast-feeding to use AMLODIPINE/VALSARTAN/HCT 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.

The safety of AMLODIPINE/VALSARTAN/HCT NOVARTIS is based on that of AMLODIPINE/VALSARTAN/HCT NOVARTIS, amlodipine/valsartan fixed dose combination tablets, and the individual components.

Adverse Reactions with Suspected Relationship to AMLODIPINE/VALSARTAN/HCT NOVARTIS
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

In the controlled trial of AMLODIPINE/VALSARTAN/HCT NOVARTIS, where only the maximum dose (10/320/25 mg) was evaluated, safety data was obtained in 582 patients with hypertension. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse reactions was not related to gender, age, or race. In the active controlled clinical trial, discontinuation due to side effects occurred in 4.0% of patients treated with AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25 mg compared to 2.9% of patients treated with valsartan/hydrochlorothiazide 320/25 mg, 1.6% of patients treated with amlodipine/valsartan 10/320 mg, and 3.4% of patients treated with hydrochlorothiazide/amlodipine 25/10 mg. The most common reasons for discontinuation of therapy with AMLODIPINE/VALSARTAN/HCT NOVARTIS were dizziness (1.0%) and hypotension (0.7%).

The adverse reactions that occurred in the active controlled clinical trial in at least 2% of patients treated with AMLODIPINE/VALSARTAN/HCT NOVARTIS but at a higher incidence in the triple combination group than in any one of the dual combinations groups are presented in the table below:

Table 1

Preferred term	**Aml/Val/HCT 10/320/25 mg N=582 n (%)**	**Val/HCT 320/25 mg N=559 n (%)**	**Aml/Val 10/320 mg N=566 n (%)**	**HCT/Aml 25/10 mg N=561 n (%)**
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)
Oedema peripheral	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)

Adverse Reactions with Suspected Relationship to Exforge (Amlodipine/valsartan)

The safety of Exforge or 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.

Table 2

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 Individual Components

Adverse reactions previously reported with one of the individual components may occur with AMLODIPINE/VALSARTAN/HCT 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.

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.

Valsartan (Diovan®): 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, dermatitis bullous, hyponatraemia, 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. Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

In rare cases, valsartan may be associated with decreases in haemoglobin and haematocrit. In controlled clinical trials, 0.8% and 0.4% of patients receiving valsartan showed significant decreases (>20%) in haematocrit and haemoglobin, respectively. In comparison, 0.1% of patients receiving placebo showed significant decreases in both haematocrit and haemoglobin.

Neutropenia was observed in 1.9% of patients treated with valsartan versus 1.6% of patients treated with an ACE inhibitor.

In heart failure patients, greater than 50% increases in creatinine 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 and 3.4% of captopril-treated patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Valsartan/hydrochlorothiazide (Co-Diovan®): Other additional adverse experiences reported with valsartan/hydrochlorothiazide combination therapy were as follows: Upper respiratory tract infection, abdominal pain upper, arthritis, bronchitis, bronchitis acute, chest pain, dyspnoea, gastroenteritis, hypoesthesia, hypokalaemia, insomnia, muscle strain, nasal congestion, neck pain, otitis media, pain in the extremity, pyrexia, sinus congestion, sinusitis, ligament sprain, urinary tract infection, viral infection, vision blurred, angioedema, serum sickness, vasculitis, renal impairment, myalgia, decrease in serum potassium, elevation in creatinine and blood urea nitrogen. There have also been reported several cases of hydrochlorothiazide-induced pulmonary oedema with

granulocytic infiltration and IgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated rare idiosyncratic reaction to hydrochlorothiazide.

Hydrochlorothiazide: Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in AMLODIPINE/VALSARTAN/HCT NOVARTIS. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Very common: Mainly at higher dose, hypokalaemia, blood lipids increased.

Common: Hyponatraemia, hypomagnesaemia, hyperuricaemia, urticaria and other forms of rash, loss of appetite, mild nausea and vomiting, postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and impotence. (see Section 4.4 Special warnings and precautions for use).

Rare: Hypercalcaemia, hyperglycaemia, glycosuria, and worsening of diabetic metabolic state, photosensitisation, abdominal distress, constipation, diarrhoea, and gastrointestinal discomfort, intrahepatic cholestasis or jaundice, cardiac arrhythmias, headache, dizziness or light-headedness, sleep disturbances, depression, paraesthesia, disturbances of vision, and thrombocytopenia, sometimes with purpura.

Very rare: Hypochloric alkalosis, necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema. Acute respiratory distress syndrome (see Section 4.4 Special warnings and precautions for use).

The following adverse drugs reactions have been identified based on post-marketing experiences. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies. Therefore frequency assigned is “not known”.

Frequency “not known”: Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma.

With hydrochlorothiazide: Frequency not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma). Based on available data from epidemiological studies, cumulative dose dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed (see also sections (see Section 4.4 Special warnings and precautions for use, and Section 5.1 Pharmacodynamic properties).

Eye disorders: Choroidal effusion, acute myopia (frequency not known). Cases of choroidal effusion with visual field defect have been reported after the use of thiazide diuretics.

Laboratory Findings

Clinical laboratory test findings were obtained in a controlled trial of AMLODIPINE/VALSARTAN/HCT NOVARTIS administered at the maximal dose of 10/320/25 mg compared to maximal doses of dual therapies, i.e. valsartan/hydrochlorothiazide 320/25 mg, amlodipine/valsartan 10/320 mg, and hydrochlorothiazide/amlodipine 25/10 mg.

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 2.1% of AMLODIPINE/VALSARTAN/HCT NOVARTIS patients compared to 2.4% of valsartan/hydrochlorothiazide patients, 0.7% of amlodipine/valsartan patients, and 1.8% of hydrochlorothiazide/amlodipine patients.

In heart failure patients, greater than 50% increases in creatinine 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 and 3.4% of captopril-treated patients.

Blood Urea Nitrogen: In hypertensive patients, greater than 50% increases in blood urea nitrogen were observed in 29.5% of AMLODIPINE/VALSARTAN/HCT NOVARTIS-treated patients compared to 29.3% of valsartan/ hydrochlorothiazide patients, 15.8% of amlodipine/valsartan patients, and 18.5% of hydrochlorothiazide/amlodipine patients. The majority of blood urea nitrogen values remained within normal limits.

In heart failure patients, greater than 50% increases in blood urea nitrogen were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in AMLODIPINE/VALSARTAN/HCT NOVARTIS-treated patients.

Serum Potassium: In hypertensive patients, greater than 20% decreases in serum potassium were observed in 6.5% of AMLODIPINE/VALSARTAN/HCT NOVARTIS-treated patients compared to 3.3% of valsartan/hydrochlorothiazide patients, 0.4% of amlodipine/valsartan patients, and 19.3% of hydrochlorothiazide/amlodipine patients. Greater than 20% increases in potassium were observed in 3.5% of AMLODIPINE/VALSARTAN/HCT NOVARTIS-treated patients compared to 2.4% of valsartan/hydrochlorothiazide patients, 6.2% of amlodipine/valsartan patients, and 2.2% of hydrochlorothiazide/amlodipine patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

4.9 OVERDOSE

Symptoms

There is no experience of overdose with AMLODIPINE/VALSARTAN/HCT NOVARTIS. 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. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

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/HCT 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 whereas clearance of hydrochlorothiazide will be achieved by dialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

AMLODIPINE/VALSARTAN/HCT NOVARTIS combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics 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/HCT 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.

Hydrochlorothiazide: The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter, which affects mechanisms of electrolyte reabsorption. Inhibition of the Na^+Cl^- symporter directly increases excretion of sodium and chloride in approximately equivalent amounts. It also indirectly reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Clinical trials

There have been no long-term, clinical outcome studies using these fixed-dose combination tablets.

AMLODIPINE/VALSARTAN/HCT NOVARTIS was studied in an 8-week double-blind, active controlled study in patients with moderate to severe essential hypertension (mean sitting diastolic blood pressure ≥100 mmHg and <120 mmHg and mean sitting systolic blood pressure ≥145 mmHg and <200 mmHg). Patients with renal or hepatic impairment, type 1 diabetes and uncontrolled type 2 diabetes, and cardiovascular conditions including heart failure requiring treatment, history of myocardial infarction, angina, revascularisation procedure, moderate or malignant retinopathy, hypertensive encephalopathy, cerebrovascular accident or transient ischemic attack were excluded from the study. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/hydrochlorothiazide 10/320/25 mg, valsartan/hydrochlorothiazide 320/25 mg, amlodipine/valsartan 10/320 mg, or hydrochlorothiazide/amlodipine 25/10 mg. At study initiation patients were assigned lower doses of their treatment combination and were titrated to their full treatment dose by week 2. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian and 17% were Black.

At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with AMLODIPINE/VALSARTAN/HCT NOVARTIS (n=571), 32.0/19.7 mmHg with valsartan/hydrochlorothiazide (n=553), 33.5/21.5 mmHg with amlodipine/valsartan (n=558) and 31.5/19.5 with amlodipine/hydrochlorothiazide (n=554). The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with AMLODIPINE/VALSARTAN/HCT NOVARTIS were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide (see Figure 1). The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of AMLODIPINE/VALSARTAN/HCT NOVARTIS (See Figure 2 and 3). Statistically significant greater proportions of patients achieved BP control (<140/90 mmHg) with AMLODIPINE/VALSARTAN/HCT NOVARTIS (71%) compared to each of the three dual combination therapies (45-54%).

Figure 1: Reduction in Mean Blood Pressure at Endpoint

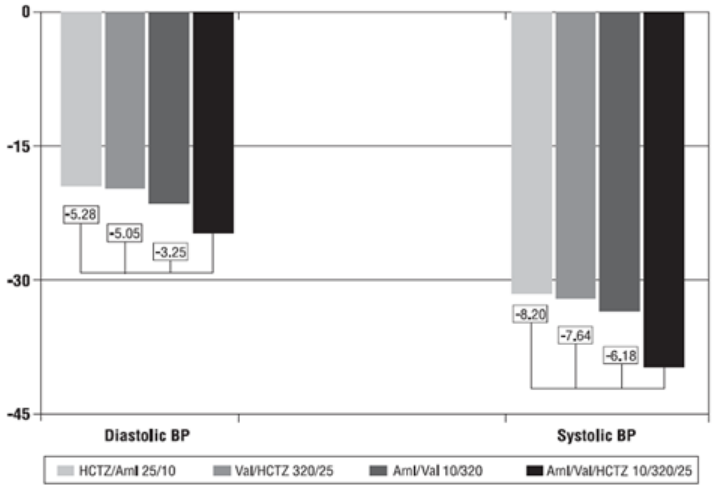


Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

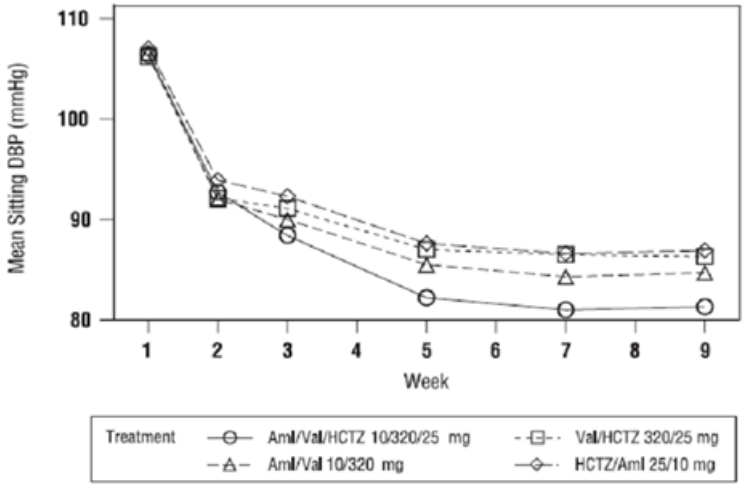
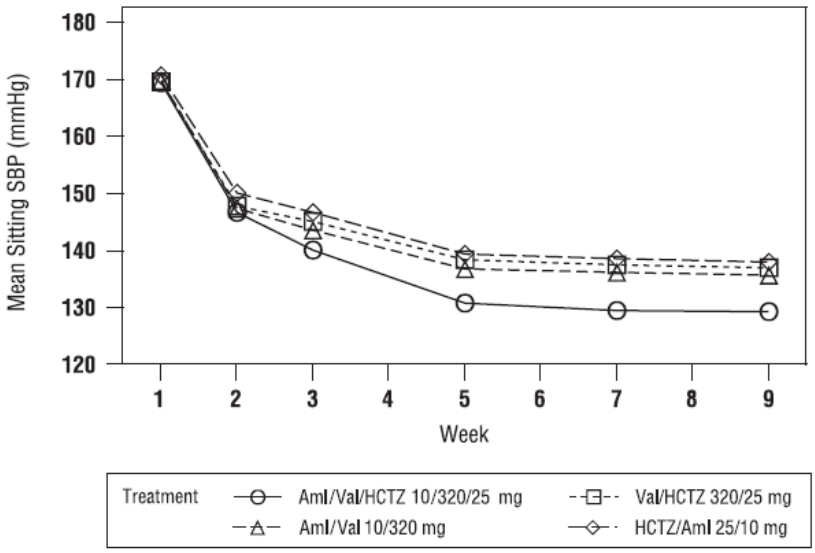


Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week



A subgroup of 268 patients was studied with ambulatory blood pressure monitoring. Clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures with the triple combination compared to valsartan/hydrochlorothiazide, amlodipine/valsartan, and hydrochlorothiazide/amlodipine were observed.

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

Similar studies have not been carried out with the lower dose strength AMLODIPINE/VALSARTAN/HCT NOVARTIS combinations.

The beneficial affects on mortality and cardiovascular morbidity are unknown.

Withdrawal and rebound effects on efficacy have not been studied.

There have been no sufficient studies carried out to support the use of this product in the context of add-on or step-up dose titration from the dual combinations (see Section 4.2 Dose and method of administration).

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed. One study included a population comprised of 71,553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and

SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). For example: A 100,000 mg cumulative dose corresponds to more than 10 years' daily use with a defined daily dose of 25 mg (see section 4.4 Special Warnings and Precautions For Use and Section 4.8 Adverse Effects (Undesirable Effects)).

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.

Hydrochlorothiazide: The absorption of hydrochlorothiazide after an oral dose is rapid (T_{max} about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated administration, and accumulation is minimal when administered once daily.

Amlodipine/valsartan/hydrochlorothiazide: Following oral administration of AMLODIPINE/VALSARTAN/HCT NOVARTIS in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from AMLODIPINE/VALSARTAN/HCT NOVARTIS are the same as when administered as individual dosage forms. The bioavailability of amlodipine, valsartan, and hydrochlorothiazide were not altered when AMLODIPINE/VALSARTAN/HCT NOVARTIS was administered with food.

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. Amlodipine crosses the placenta and is excreted into breast milk.

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 30 L/h).

Hydrochlorothiazide: The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6-15 hours. Greater than 95% of the absorbed dose is excreted as unchanged compound in the urine.

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

Pharmacokinetics in the elderly: 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.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Since the three components are equally well tolerated in younger and elderly patients, no dosage adjustment of AMLODIPINE/VALSARTAN/HCT NOVARTIS is necessary in elderly 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.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

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 - Impaired hepatic function). There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see Section 4.3 Contraindications).

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

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 and hydrochlorothiazide combination. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity with generally negative results.

Amlodipine: 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*).

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*.

Hydrochlorothiazide: Hydrochlorothiazide did not induce gene mutation in bacteria or chromosome damage in mammalian cells in several *in vitro* and *in vivo* assays. However positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in *Aspergillus nidulans*). Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine

dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that there is no relevant mutagenic potential in vivo, although hydrochlorothiazide could enhance the genotoxic effects of UVA light.

Carcinogenicity

No carcinogenicity studies have been conducted with the amlodipine, valsartan and hydrochlorothiazide combination. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for carcinogenicity with generally negative results.

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.

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 (160 mg bid).

Hydrochlorothiazide: Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide alone at approximately 600 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline-cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, macrogol 4000, purified talc, iron oxide yellow (except 5/160/12.5) and iron oxide red (10/160/12.5 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/HCT NOVARTIS 5/160/12.5® (5 mg amlodipine, 160 mg valsartan and 12.5 mg hydrochlorothiazide): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/12.5® (10 mg amlodipine, 160 mg valsartan and 12.5 mg hydrochlorothiazide): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 5/160/25® (5 mg amlodipine, 160 mg valsartan and 25 mg hydrochlorothiazide): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/160/25® (10 mg amlodipine, 160 mg valsartan and 25 mg hydrochlorothiazide): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

AMLODIPINE/VALSARTAN/HCT NOVARTIS 10/320/25® (10 mg amlodipine, 320 mg valsartan and 25 mg hydrochlorothiazide): PA/Al/PVC/Al blister packs of 7, 14, 28, 30 and 56.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

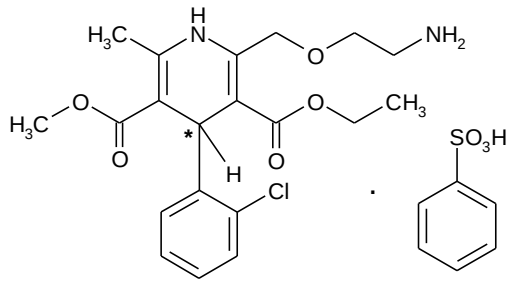
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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. Hydrochlorothiazide is a white or almost white powder, very slightly soluble in water and freely soluble in dimethylsulfoxide.

Active ingredients (INN): amlodipine besylate, valsartan and hydrochlorothiazide

Chemical structure



and enantiomer

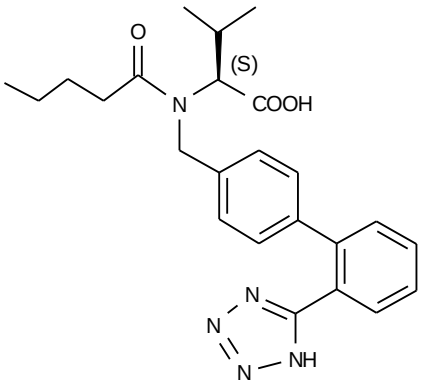
Amlodipine (as the besylate salt)

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

CAS number: 111470-99-6

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

Molecular weight: 567.06



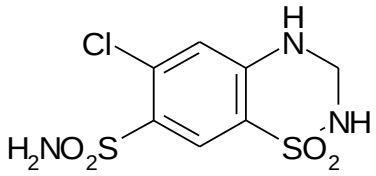
Valsartan

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

CAS : 137862-53-4

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

Molecular weight: 435.5



Hydrochlorothiazide

(6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide)

CAS number: 58-93-5

Molecular formula: $C_7H_8ClN_3O_4S_2$

Molecular weight: 297.72

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

9 April 2010

10 DATE OF REVISION

27 October 2022

® = Registered Trademark

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of acute respiratory distress syndrome as a precaution for hydrochlorothiazide-containing medicines
4.8	Addition of acute respiratory distress syndrome as a very rare AE for hydrochlorothiazide-containing medicines

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Internal document code: vah271022i based on CDS dated 10-Sep-2018.