AUSTRALIAN PRODUCT INFORMATION

DILART

Valsartan

1 NAME OF THE MEDICINE

Valsartan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg, 80 mg, 160 mg or 320 mg of valsartan as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Dilart 40 mg tablet	:	Yellow, oval shaped, biconvex, film coated tablets debossed with “VN” and “1” on either side of the score line on one side and “M” on the other side.
Dilart 80 mg tablet	:	Pale red, round, biconvex, bevelled edge, film-coated tablets having a score line on one side and debossed with "M" over "VN 2" on other side.
Dilart 160 mg tablet	:	Beige, oval-shaped, biconvex, bevelled edge, film-coated tablets debossed with "M" to the left of the score on one side and "VN 3" on the other side of the tablet.
Dilart 320 mg tablet	:	Dark grey, oval shaped, biconvex, film coated tablets debossed with “VN 4” on one side and “M” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Treatment of hypertension.
- Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy (e.g. diuretics, digitalis) who are intolerant to ACE inhibitors.
- To improve survival following myocardial infarction in clinically stable patients with clinical or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension

The recommended dose of valsartan is 80 mg once daily, irrespective of race, age or gender. The maximum antihypertensive effect is seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 160 mg. If additional blood pressure reduction is required, a diuretic may be added or the dose can be increased further to a maximum of 320 mg. Valsartan may also be administered with other antihypertensive agents.

Heart failure

The recommended starting dose of valsartan is 40 mg twice daily. Titration upwards to 80 mg and 160 mg twice daily should be done to the highest dose tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

An assessment of renal function should always be conducted in patients with heart failure.

Valsartan has not been demonstrated to reduce mortality in patients with cardiac failure. No additional benefit on morbidity has been demonstrated from the concurrent use of valsartan and ACE inhibitors. Concurrent use of valsartan and an ACE inhibitor is not recommended.

Post-myocardial infarction

Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan therapy should be titrated to 40 mg, 80 mg and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.

Achievement of the target dose of 160 mg twice daily should be based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers and statins.

Valsartan should be administered consistently with or without food (see Section 5.2 PHARMACOKINETIC PROPERTIES – Absorption).

No initial dosage adjustment is required in the elderly.

Use in patients with renal impairment

For patients with severe renal impairment, a maximum daily dose of 80 mg per day is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Impaired renal function and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in patients with mild to moderate hepatic impairment

A daily dose of 80 mg should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRESCAUTIONS FOR USE – Impaired hepatic function and Section 5.2 PHARMACOKINETIC PROPERTIES). Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take valsartan (see Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

- Hypersensitivity to any of the components of Dilart
- Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy).
- Severe hepatic impairment; biliary cirrhosis and cholestasis
- 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

Use in special patient groups

Sodium-and/or volume-depleted patients

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan. Sodium and/or volume depletion should be corrected before starting treatment with valsartan, for example, by reducing the diuretic dose or treatment should be commenced under close medical supervision.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment with valsartan can be continued once the blood pressure has stabilised.

Renal artery stenosis

There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis. 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.

Hepatic injury

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

Heart failure/post-myocardial infarction

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.

Concomitant therapy in patients with heart failure

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 (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

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. Valsartan should be immediately discontinued in patients who develop angioedema, and 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).

Patients receiving potassium-sparing diuretics or potassium-containing products

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, trimethoprim containing medicines etc.) may lead to increases in serum potassium. If concomitant medication is considered necessary, monitoring of serum potassium is advised (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Use in Hepatic Impairment

In patients with mild to moderate hepatic impairment without cholestasis, valsartan should be used with caution (see Section 5.2 PHARMACOKINETIC PROPERTIES – Impaired hepatic function). The daily dose of valsartan should not exceed 80 mg. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take valsartan (see Section 4.3 CONTRAINDICATIONS).

Use in Renal Impairment

In patients with severe renal impairment (creatinine clearance < 30 mL/minute) the dose of valsartan should not exceed 80 mg per day.

The use of angiotensin receptor antagonists (ARBs) including valsartan or angiotensin converting enzyme inhibitors (ACEIs) with aliskiren should be avoided in patients with severe renal impairment (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, increases of blood urea and serum creatinine and changes in renal function including renal failure (very rarely) have been reported, particularly in patients with pre-existing renal dysfunction or those with severe cardiac insufficiency. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure) treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) acute renal failure and/or death. It cannot be excluded that valsartan could behave similarly.

Use in the Elderly

In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population.

Of the 2,511 patients with heart failure randomised to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years or older. No special precautions are required when using valsartan in elderly patients with heart failure.

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 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.

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 monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on valsartan 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 should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (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).

Potassium

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, trimethoprim containing medicines etc) may lead to increases in serum potassium and in heart failure patients, may lead to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in special patient groups).

Lithium salts

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including valsartan. 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 valsartan.

Hepatic Transporters

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

No drug interactions of clinical significance have yet been found. Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide (frusemide), digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine and 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, furosemide (frusemide) and warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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.

Use in Pregnancy

Pregnancy Category: D
Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause fetal 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).

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. As for any drug that also acts directly on the RAAS, valsartan should not be used during pregnancy (see Section 4.3 CONTRAINDICATIONS) or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. When pregnancy is detected, valsartan should be discontinued as soon as possible.

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. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

No teratogenic effects were observed when valsartan 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, fetal losses were observed at the highest dose level in rabbits, and fetal 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 postnatal 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.

Use in Lactation

Although valsartan is excreted in the milk of lactating rats, it is not known whether it is excreted in human milk. A perinatal/postnatal study in rats 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 oral dose levels greater than 200 mg/kg/day. Thus, it is not advisable to use valsartan in breast-feeding mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following summary of adverse reactions (Table 1) is based on clinical trials in hypertension, heart failure and post-myocardial infarction treated with various doses of valsartan (10 mg - 320 mg daily). It also includes post-marketing reports. The incidence of reported adverse events (AEs) in clinical trials did not appear to be related to dose or duration of treatment.

Therefore, AEs occurring on all doses of valsartan were pooled. As well, the incidence of AEs was not associated with gender, age or race.

Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10 000, <1/1000); very rare (<1/10 000).

Table 1: Adverse reaction summary from clinical trials and post-marketing reports

Infections and infestations	
Common:	Viral infections
Uncommon:	Upper respiratory tract infection, pharyngitis, sinusitis
Very rare:	Rhinitis
Blood and lymphatic system disorders	
Common:	Neutropenia

Very rare:	Thrombocytopenia
Immune system disorders	
Very rare:	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Common:	Hyperkalaemia*#
Psychiatric disorders	
Uncommon:	Insomnia, libido decrease
Nervous system disorders	
Common:	Postural dizziness#
Uncommon:	Syncope*
Rare:	Dizziness##
Very rare:	Headache##
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Cardiac failure*
Vascular disorders	
Common:	Orthostatic hypotension*
Uncommon:	Hypotension*##
Very rare:	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough
Gastrointestinal disorders	
Uncommon:	Diarrhoea, abdominal pain
Very rare:	Nausea##
Skin and subcutaneous tissue disorders	
Very rare:	Angioneurotic oedema**, rash, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Back pain
Very rare:	Arthralgia, myalgia
Renal and urinary disorders	
Very rare:	Renal impairment**##, acute renal failure**, renal insufficiency**
General disorders and administration site conditions	
Uncommon:	Fatigue, asthenia, oedema

*reported in post-myocardial infarction indication; # reported in heart failure indication

** Reported as uncommon in post-myocardial infarction ## reported more frequently in heart failure indication (common: dizziness, renal impairment, hypotension; uncommon: headache, nausea).

Hypertension

In placebo-controlled trials in which 2,542 patients with hypertension were treated with various doses of valsartan (10 mg – 320 mg), the study drug showed an overall incidence of adverse events (AEs) comparable with that of placebo.

A 6-month open-label extension trial involving 642 patients with hypertension treated with valsartan 320 mg showed an overall incidence of AEs comparable with that observed in placebo-controlled trials.

All adverse events with an incidence of 1% or more in the valsartan treatment group are included in Table 2, irrespective of their causal association with the study drug.

Table 2: Adverse events with an incidence of 1% or more in the valsartan treatment group V Placebo.

	Valsartan (n=2542) %	**Placebo (n=1007) %**
Nervous system:		
Headache	9.8	13.6
Dizziness	3.7	3.9
Infections and infestations:		
Viral infection	3.3	2.6
Respiratory system:		
Upper respiratory tract infection	2.6	2.3
Coughing	2.4	1.3
Rhinitis	1.9	2.0
Sinusitis	1.8	1.7
Pharyngitis	1.2	0.7
Gastrointestinal tract:		
Diarrhoea	2.4	1.6
Abdominal pain	1.6	0.9
Nausea	1.6	2.2
Body as a whole:		
Fatigue	2.2	1.3
Musculoskeletal system:		
Back pain	1.7	1.5
Arthralgia	1.0	1.0

Other adverse experiences that occurred in controlled clinical trials of patients treated with valsartan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to valsartan.

Cardiovascular: Palpitations

Gastrointestinal: Constipation, dry mouth, dyspepsia and flatulence

Musculoskeletal: Muscle cramps

Neurologic and psychiatric: Anxiety, paraesthesia and somnolence

Respiratory: Dyspnoea

Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia and vomiting.

Heart failure

The adverse experience profile of valsartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial (Val-HeFT), comparing valsartan in total daily doses up to 320 mg (n = 2,506) to placebo (n = 2,494), 9.9% of valsartan patients discontinued for adverse events vs. 7.3% of placebo patients.

Table 2 above includes adverse reactions from double blind short term heart failure trials, including the first 4 months of the ValHeFT, and drug-related adverse events with an incidence greater than 1% and more frequent in valsartan treated patients than in placebo treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

Post-myocardial infarction

In the double-blind, randomised, active-controlled, parallel-group VALIANT trial comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction, the safety profile of valsartan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting.

Serious adverse events (SAEs) were primarily cardiovascular and generally related to the underlying disease as reflected in the primary efficacy endpoint of all-cause mortality. Nonfatal SAEs with suspected study drug relationship observed with an incidence of ≥0.1% are included in Table 5 below.

The percentage of permanent discontinuations due to adverse events was 5.8% in valsartan-treated patients and 7.7% in captopril-treated patients. Permanent discontinuation for hypotension or renal adverse events occurred in 1.4% and 1.1%, respectively, of valsartan-treated patients, and in 0.8% and 0.8%, respectively, of captopril-treated patients.

Post-marketing experience

Elevated liver enzymes and very rare reports of hepatitis. Angioedema and rash have been reported rarely. Pruritus and other hypersensitivity/allergic reactions including serum sickness and vasculitis have been reported very rarely. There have been very rare cases of bleeding and thrombocytopenia. Very rare cases of impaired renal function have also been reported. Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers. Dermatitis bullous and hyponatraemia of unknown incidence have been reported.

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.

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.

4.9 OVERDOSE

Symptoms

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment

The patient should always be given a sufficient amount of activated charcoal. Otherwise, the usual treatment would be intravenous infusion of normal saline solution. Valsartan is not 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

Mechanism of Action

The active hormone of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through the action of angiotensin converting enzyme (ACE). Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Dilart (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. When valsartan is combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In multiple dose studies in hypertensive patients valsartan had no notable effects on total cholesterol, fasting triglycerides, or fasting serum glucose. Valsartan has no uricosuric effect.

Heart failure

Hemodynamics and plasma neurohormones were measured in NYHA class II-IV heart failure patients with pulmonary capillary wedge pressure ≥15 mmHg in 2 short-term, chronic therapy studies. In one study, which included patients chronically treated with ACE inhibitors, single and multiple doses of valsartan given in combination with an ACE inhibitor improved hemodynamics including pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and systolic blood pressure (SBP). Reductions were observed in plasma aldosterone (PA) and plasma norepinephrine (PNE) levels after 28 days of treatment. In the second study, which included only patients untreated with ACE inhibitors for at least 6 months prior to enrollment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment. In the long-term Valsartan Heart Failure Trial, plasma norepinephrine and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Clinical Trials

Hypertension

Treatment with Valsartan 320 mg

A randomised, double-blind, multi-centre, active-controlled, parallel-group study in patients with hypertension was designed to evaluate the efficacy and safety of once daily dose of valsartan 320 mg (n = 1,873) compared to valsartan 160 mg (n = 1,884) after a 4 week run-in period with valsartan 160 mg once daily. Blood pressure lowering effects of 4 weeks treatment were measured in patients aged 18-80 years with uncomplicated mild to moderate hypertension (mean sitting diastolic blood pressure [MSDBP] ≥ 95 mmHg and ≤109 mmHg). Patients with severe or malignant hypertension, those who were unable to cease all antihypertensive agents for 2 weeks and those who had a clinically significant disorder that might affect study outcome or patients safety were excluded from participation in this study.

The primary efficacy measure was change in trough MSDBP from baseline to endpoint, and the secondary efficacy measure was changes in trough MSDBP from baseline to endpoint in patients not adequately controlled with valsartan 160 mg.

Results for both MSDBP and mean sitting diastolic blood pressure (MSSBP) are reported in Tables 3 and 4.

Table 3 Between-treatment comparisons of MSDBP and MSSBP (mmHg) at endpoint (study H2301 - overall ITT population)

	Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
MSDBP	Valsartan 320 mg vs. 160 mg	-1.18(0.23)	(-1.63;-0.72)	<0.0001
MSSBP	Valsartan 320 mg vs. 160 mg	-2.59(0.40)	(-3.38;-1.81)	<0.0001

Note: Results were from an ANCOVA model containing centre, treatment and responder stratum

Table 4 Between-treatment comparison of MSDBP and MSSBP (mmHg) at endpoint in non-responders (study H2301)

	Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
MSDBP	Valsartan 320 mg vs. 160 mg	-1.29(0.32)	(-1.91;-0.66)	<0.0001
MSSBP	Valsartan 320 mg vs. 160 mg	-2.46(0.57)	(-3.58;-1.34)	<0.0001

Note: Results were from an ANCOVA model containing centre and treatment.

Heart Failure

The Valsartan Heart Failure Trial was a randomised, controlled multinational clinical trial of valsartan compared with placebo on morbidity and mortality in NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF < 40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m^2. The study enrolled 5,010 patients in 16 countries who were randomised to receive either valsartan or placebo in addition to all other appropriate therapy including ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose in the study was 254 mg. The study had two primary endpoints: all-cause mortality (time to death) and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalisation.

In the trial population no statistically significant improvement in mortality was observed among valsartan treated patients compared to those who received placebo. Morbidity was significantly reduced by 13.2% with valsartan compared to placebo treatment. The primary benefit was a 27.5% reduction in the risk for time to first heart failure hospitalisation. There was no evidence of additional benefit from concurrent use of valsartan with ACE inhibitors. An increased rate of mortality was observed in patients taking the triple combination of a beta-blocker, an ACE inhibitor and valsartan.

Valsartan-treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnea, fatigue, oedema and rales compared to placebo. Patients on valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan-treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

Post-myocardial infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤ 40% by radionuclide ventriculography or ≤ 35% by echocardiography or ventricular contrast angiography). Patients with systolic blood pressure below 100 mmHg, serum creatinine above 221 micromole/L (2.5 mg/dL), and significant right ventricular myocardial infarction were excluded.

Patients were randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan given 4–8 days (median 6 days) after myocardial infarction, captopril given 4–8 days (median 6 days) after myocardial infarction, or the combination of both. Physicians were advised to titrate patients up to at least 80 mg valsartan twice daily at 15 days after randomisation or at hospital discharge, and that the target maximum dose of 160 mg valsartan twice daily should be reached after 3 months. The mean treatment duration was two years. The mean daily dose of valsartan in the monotherapy group was 217 mg. Baseline therapy included acetylsalicylic acid (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%) and statins (34%). The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction, as summarised in Table 5 below. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

Table 5: Efficacy results: primary and secondary endpoints from the VALIANT study

	Valsartan N=4,909	**Captopril N=4,909**	**Valsartan + Captopril N=4,885**
Primary Endpoint			
Number of deaths (%)	979 (19.9%)	958 (19.5%)	941 (19.3%)
Secondary Endpoints			
Cardiovascular mortality	827 (16.8%)	830 (16.9%)	827 (16.9%)
Cardiovascular mortality, hospitalisation for heart failure, and recurrent non-fatal myocardial infarction (composite endpoint)	1529 (31.1%)	1567 (31.9%)	1518 (31.1%)
Cardiovascular mortality, hospitalisation for heart failure, and recurrent non-fatal myocardial infarction, non-fatal stroke and cardiac arrest with resuscitation (composite endpoint)	1612 (32.8%)	1641 (33.4%)	1580 (32.3)

No statistically significant differences between the treatment groups were observed.

Since this was a trial with an active control (captopril), an additional analysis of all-cause mortality was performed to estimate how valsartan would have performed versus placebo. Using the results of the previous reference myocardial infarction trials – SAVE, AIRE, and TRACE – the estimated effect of valsartan preserved 99.6% of the effect of captopril (97.5% CI = 60–139%). Combining valsartan with captopril did not add further benefit over captopril alone, therefore this combination is not recommended. There was no difference in all-cause mortality based on age, gender, race, baseline therapies or underlying disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 hours post-dosing, plasma valsartan concentrations are similar for the fed and fasted group.

Distribution

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

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

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/hour) when compared with hepatic blood flow (about 30 L/hour).

Effect of age and disease on pharmacokinetics

Elderly patients

Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Children

The pharmacokinetics of valsartan have not been investigated in patients less than 18 years of age.

Heart failure

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/hour. Age does not affect the apparent clearance in heart failure patients.

Impaired renal function

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.

Impaired hepatic function

About 70% of the absorbed 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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genetic toxicology 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*.

Carcinogenicity

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 concentrations approximately 1.5 times the concentrations achieved in humans at the maximum recommended dose (160 mg bid).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets: microcrystalline cellulose, crospovidone, colloidal anhydrous silica, Croscarmellose sodium, povidone, magnesium stearate, hypromellose, titanium dioxide, macrogol 8000, iron oxide red (valsartan 80 mg,160 mg and 320 mg tablets only), iron oxide yellow . Valsartan 40 mg, 160 mg and 320 mg tablets also contain iron oxide black.

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Dilart 40 mg tablet	:	Container type: OPA/Al/PVC/Al or Aluminium/PVC/PE/PVDC Pack sizes: blister packs and bottles of 28* and 30.
Dilart 80 mg tablet	:	Container type: OPA/Al/PVC/Al or Aluminium/PVC/PE/PVDC Pack sizes: blister packs and bottles of 28* and 30.
Dilart 160 mg tablet	:	Container type: OPA/Al/PVC/Al or Aluminium/PVC/PE/PVDC Pack sizes: blister packs and bottles of 28* and 30.
Dilart 320 mg tablet	:	Container type: OPA/Al/PVC/Al or Aluminium/PVC/PE/PVDC Pack sizes: blister packs and bottles of 28* and 30.

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

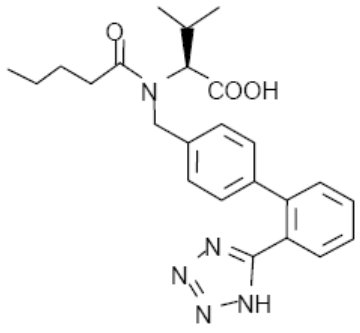
6.7 PHYSICOCHEMICAL PROPERTIES

Valsartan is a white to practically white fine powder.

Chemical Structure

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

Structural formula :



Molecular formula : $C_{24}H_{29}N_5O_3$ Molecular weight : 435.5

It is soluble in ethanol and methanol and slightly soluble in water.

CAS Number

137862-53-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd
Level 1, 30 The Bond
30-34 Hickson Road
Millers Point NSW 2000
www.mylan.com.au

9 DATE OF FIRST APPROVAL

26/08/2014

10 DATE OF REVISION

19/06/2020

Summary Table of Changes

Section Changed	Summary of New Information
4.2	Addition of relevant section references.
4.4	Addition of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels.
4.5	Addition of other drugs that may increase potassium levels.
4.9, 8	Minor editorial changes.

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