AUSTRALIAN PRODUCT INFORMATION

DIOVAN® 40 (VALSARTAN) FILM-COATED TABLET
DIOVAN® 80 (VALSARTAN) FILM-COATED TABLET
DIOVAN® 160 (VALSARTAN) FILM-COATED TABLET
DIOVAN® 320 (VALSARTAN) FILM-COATED TABLET

1 NAME OF THE MEDICINE

Valsartan.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Diovan is:

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

(INN = valsartan). Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

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

3 PHARMACEUTICAL FORM

Diovan 40 mg tablet: Film-coated tablet containing 40 mg valsartan; yellow, ovaloid, scored on one side with "DO" on scored side and "NVR" on other side.

Diovan 80 mg tablet: Film-coated tablet containing 80 mg valsartan; pale red, round, scored on one side with "D/V" on scored side and "NVR" on other side.

Diovan 160 mg tablet: Film-coated tablet containing 160 mg valsartan; grey-orange, ovaloid, scored on one side with "DX/DX" on scored side and "NVR" on other side.

Diovan 320 mg tablet: Film-coated tablet containing 320 mg valsartan; grey-violet, ovaloid, with "DXL" on one side and "NVR" on 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 5.2 PHARMACOKINETIC PROPERTIES -Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension: The recommended dose of Diovan 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. Diovan may also be administered with other antihypertensive agents.

Heart failure: The recommended starting dose of Diovan 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.

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

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 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 PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES). Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take Diovan (see Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

- Hypersensitivity to any of the components of Diovan;
- Pregnancy (see "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 Diovan. Sodium and/or volume depletion should be corrected before starting treatment with Diovan, 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 Diovan can be continued once the blood pressure has stabilised.

Renal artery stenosis: There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis. Short-term administration of Diovan 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.

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

The use of angiotensin receptor antagonists (ARBs) including Diovan 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 Diovan could behave similarly.

Impaired hepatic function: 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 Diovan (see Section 4.3 CONTRAINDICATIONS).

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 Diovan 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 5.2 PHARMACOKINETIC 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. Diovan 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 Diovan, 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 Diovan 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).

Elderly patients: In the controlled clinical trials of valsartan, 1214 (36.2 %) of hypertensive patients treated with valsartan were $\geq$ 65 years and 265 (7.9 %) were $\geq$ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population.

Of the 2511 patients with heart failure randomised to valsartan in the Valsartan Heart Failure Trial, 45% (1141) were 65 years or older. No special precautions are required when using valsartan in elderly patients with heart failure.

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

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 Diovan, 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 Diovan and other agents that affect the RAS (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The concomitant use of ARBs including Diovan, 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 Diovan, 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 Diovan. 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 Diovan.

Hepatic Transporters:

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

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

As Diovan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies

have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, frusemide and warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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, Diovan 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, Diovan 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 peri/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 Diovan 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)

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 following summary of adverse reactions (Table 3) 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 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 3: 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: headeache, nausea)

Hypertension

In placebo-controlled trials in which 2542 patients with hypertension were treated with various doses of Diovan (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 Diovan 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 Diovan treatment group are included in the following table, irrespective of their causal association with the study drug.

	Diovan (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 Diovan (> 0.2 % of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

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 Diovan 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=2506) to placebo (n=2494), 9.9% of valsartan patients discontinued for adverse events vs. 7.3% of placebo patients.

Table 3 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. Non-fatal SAEs with suspected study drug relationship observed with an incidence of ≥0.1% are included in Table 3 above.

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 Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan 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 Diovan 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 Diovan 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 Diovan treated patients compared to 5.1% of placebo treated patients.

4.9 OVERDOSE

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

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.

Diovan (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 Diovan 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 Diovan 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.

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 Diovan 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.

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.

Elimination:

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).

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/h. 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").

Clinical trials

Hypertension

Treatment with Diovan 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=1873) compared to valsartan 160 mg (n=1884) after a 4 week run-in period with valsartan 160 mg o.d. 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] $\geq$ 95 mmHg and $\leq$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 1 and 2.

Table 1 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 160 mg	320 mg	vs.	-1.18 (0.23)	(-1.63; -0.72)	<0.0001
MSSBP	valsartan 160 mg	320 mg	vs.	-2.59 (0.40)	(-3.38; -1.81)	<0.0001

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

Table 2 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 160 mg	320 mg	vs.	-1.29 (0.32)	(-1.91; -0.66)	<0.0001
MSSBP	valsartan 160 mg	320 mg	vs.	-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 5010 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 $\leq 40\%$ by radionuclide ventriculography or $\leq$ 35% by echocardiography or ventricular contrast angiography). Patients with systolic blood pressure below 100 mm Hg, serum creatinine above 221 mcmol/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 Diovan 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 the table 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).

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.

5.3 PRECLINICAL SAFETY DATA

Mutagenesis, carcinogenesis and impairment of fertility:

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). 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*.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cellulose microcrystalline, crospovidone, silica-colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide, macrogol 8000, iron oxide red CI77491, iron oxide yellow CI77492. Diovan 40 mg, 160 mg and 320 mg tablets also contain iron oxide black CI77499.

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

Diovan 40 mg tablet: blister packs of 7, 28 and 56.

Diovan 80 mg tablet: blister packs of 7, 28 and 56.

Diovan 160 mg tablet: blister packs of 7, 28 and 56.

Diovan 320 mg tablet: blister packs of 7, 28 and 56.

Not all strengths and pack sizes may be marketed.

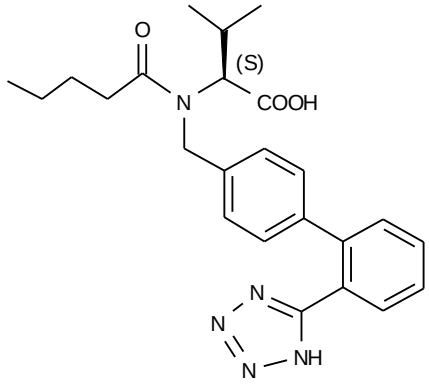
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Active ingredient: Valsartan

Chemical structure



Valsartan

CAS number: 137862-53-4

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

Molecular weight: 435.5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

13 November 2001

10 DATE OF REVISION

14 February 2020

®= Registered Trademark

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI re-formatted as per TGA form for PI March 2018
4.4	Addition of trimethoprim containing medicines to precaution on Serum electrolyte changes
4.5	Addition of trimethoprim containing medicines

8	Update of sponsor address

(dvn140220i based on CDS dated 03-Dec-2014 and TGA SIU request 7 June 2019)