

DIOVAN[®]

(valsartan)

40 mg, 80 mg, 160 mg film-coated tablets

Prescribing Information

1 Name of the medicinal product

Diovan[®] 40 mg, 80 mg and 160 mg film coated tablets.

2 Qualitative and quantitative composition

Active substance: (S)-N-valeryl-N-{{2'-(1H-tetrazol-5-yl)biphenyl-4-yl}methyl}-valine (INN = valsartan).

One tablet contains 40 mg, 80 mg or 160 mg valsartan.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Film-coated tablet.

Diovan 40 mg: Yellow, ovaloid with bevelled edges, scored on one side; with debossing "DO" on the scored side and "NVR" on the other side.

Diovan 80 mg: Pale red, round with bevelled edges, scored on one side; with debossing "D/V" on the scored side and "NVR" on the other side.

Diovan 160 mg: Grey-orange, ovaloid. One side with debossing "DX" and "NVR" on the other side.

4 Clinical particulars

4.1 Therapeutic indications

Hypertension (Diovan 80 mg and 160 mg)

Treatment of hypertension.

Heart failure (Diovan 40 mg, 80 mg and 160 mg)

Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor.

Post-myocardial infarction (Diovan 40 mg, 80 mg and 160 mg)

Diovan is indicated to improve survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see section 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Hypertension

The recommended dose of Diovan is 80 mg once daily for most patients. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose may be increased to 160 mg, or a greater decrease in BP may be achieved by adding in a thiazide diuretic.

Diovan may also be administered with other antihypertensive agents.

Use in patients over 75 years:

A lower starting dose of 40 mg once daily is recommended.

Use in renal impairment:

No initial dose adjustment is required in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine less than 20 ml/min) or patients on dialysis, a lower starting dose of 40 mg once daily is recommended.

Use in patients with intravascular volume depletion:

For those patients who have intravascular volume depletion (e.g. those treated with high dose diuretics who are unable to have their dose of diuretic reduced) a starting dose of 40 mg is recommended.

Use in patients with mild to moderate hepatic impairment:

Treatment should commence at a dose of 40 mg once daily. A daily dose of 80 mg should not be exceeded. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Diovan (see Section 4.3 Contraindications).

Use in Children and adolescents

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

Heart failure

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration 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.

Evaluation of patients with heart failure should always include assessment of renal function.

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 occur, consideration should be given to a dosage reduction.

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

Use in renal impairment:

In the indication of post myocardial infarction no dosage adjustment is required for patients with mild to moderate renal impairment. There are currently no data available in post myocardial patients with severe renal impairment (serum creatinine ≥ 221 $\mu\text{mol/l}$). Diovan should therefore be used with caution in such patients, with appropriate assessment of renal function (see Section 4.4 Special Warnings and Precautions).

Use in patients with mild to moderate hepatic impairment:

Doses higher than 80mg twice daily should only be considered if the clinical benefit is likely to outweigh the possible risk associated with increased exposure of valsartan. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Diovan (see Section 4.3 Contraindications).

Use in children and adolescents

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

4.3 Contraindications

Known hypersensitivity to valsartan or to any of the excipients of Diovan.

Pregnancy and lactation (see section 4.6 Pregnancy and lactation).

Severe hepatic impairment, cirrhosis, biliary obstruction.

4.4 Special warnings and precautions for use

Hypertension:

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. For those patients whose diuretic dose cannot be reduced in order to correct their sodium and/or volume depletion a starting dose of 40 mg is recommended.

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 is recommended as a safety measure.

Hepatic impairment:

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of valsartan in mild to moderately hepatically impaired patients, a lower dose is recommended in patients with hypertension (see Section 4.2 Posology and method of administration). In these patients the dose of 80 mg should not be exceeded. Patients with severe hepatic impairment, cirrhosis, biliary obstruction are contra-indicated from using Diovan (see Section 4.3 Contraindications).

Renal Function Impairment:

As a consequence of inhibiting the renin-aldosterone-angiotensin 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.

Serum potassium should be monitored in renally impaired or elderly patients if they are also taking potassium supplement (see section 4.8 Undesirable effects).

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 Diovan therapy because of

continuing symptomatic hypotension is not usually necessary if the dosing instructions are followed.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction (see section 4.2 Posology and method of administration).

As a consequence of the inhibition of the RAAS, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Use in hepatic impairment:

Based on pharmacokinetic data which demonstrate approximately 2-fold increases in plasma concentrations of valsartan in mild to moderately hepatically impaired patients, doses higher than 80mg twice daily should only be considered if the clinical benefit is likely to outweigh the possible risk associated with increased exposure of valsartan (see section 4.2 Posology and method of administration). Patients with severe hepatic impairment, cirrhosis, biliary obstruction are contra-indicated from using Diovan (see section 4.3 Contraindications).

Heart failure

Particular caution is called for when using the triple combination of an ACE inhibitor, a beta blocker and valsartan, since the incidence of heart failure-related morbidity and mortality was found to be higher with concomitant administration of beta blockers and ACE inhibitors than with placebo.

4.5 Interaction with other medicinal products and other forms of interaction

Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Used together with cimetidine, the systemic exposure of valsartan may be marginally increased. A combination with glibenclamide may cause a decrease in the systemic exposure to valsartan.

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, furosemide, and warfarin.

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. Comedication is not advisable.

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors,

acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and valsartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

4.6 Pregnancy and lactation

Pregnancy

Due to the mechanism of action of angiotensin II antagonists, a risk factor for the fetus cannot be excluded. *In utero* exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. 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. Healthcare professionals prescribing Diovan should counsel women of childbearing potential about the potential risk of this product during pregnancy. If pregnancy is detected during therapy, Diovan should be discontinued as soon as possible.

Lactation

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Thus, it is not advisable to use Diovan in lactating mothers.

4.7 Effects on ability to drive and use machines

There are no data to suggest that Diovan affects the ability to drive or use machines. When driving vehicles or operating machines, it should be recognized that occasionally dizziness or weariness may occur during treatment with any antihypertensive agent.

4.8 Undesirable effects

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post marketing experience and laboratory findings are listed below according to system organ class.

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

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a “not known” frequency.

Hypertension

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Elevations of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, elevation of serum creatinine
General disorders and administration site conditions	
Uncommon	Fatigue

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: arthralgia, asthenia, back pain, diarrhoea, dizziness headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Post-myocardial infarction and/or heart failure

The safety profile seen in controlled clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below.

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Not known	Increase of serum potassium
Nervous system disorders	
Common	Dizziness, postural dizziness
Uncommon	Syncope, headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, diarrhoea
Hepato-biliary disorders	
Not known	Elevations of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue

The following events have also been observed during clinical trials in patients with post-myocardial infarction and/or heart failure irrespective of their causal association with the study drug: arthralgia, abdominal pain, back pain, insomnia, libido decrease, neutropenia, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infarction, viral infections.

4.9 Overdose

Overdosage with Diovan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting

should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution.

Valsartan is unlikely to be removed by haemodialysis.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists, , (valsartan) ATC code: C09C A03.

The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular 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 AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. The AT₂ subtype is unrelated to cardiovascular effects. Valsartan does not exhibit any partial agonist activity at the AT₁ receptor and has much (about 20,000 fold) greater affinity for the AT₁ receptor than for the AT₂ 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 ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% 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 to 68.5% 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.

Hypertension

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 of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. 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, fasting serum glucose, or uric acid.

Heart failure

Haemodynamics and neurohormones. Haemodynamics 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 haemodynamics 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 noradrenalin (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 enrolment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment. In the long-term Val-HeFT study, plasma noradrenalin and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Morbidity and mortality. Val-HeFT 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/m². 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 of Diovan in Val-HeFT was 254 mg. The study had 2 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. All cause mortality was similar in the valsartan and placebo groups. Morbidity was significantly reduced by 13.2% with valsartan compared with placebo. The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalisation. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. However, risk reductions favouring placebo were observed for those patients treated with the triple combination of a beta blocker, an ACE inhibitor and valsartan. Further studies such as VALIANT (see section on Post-myocardial infarction), where mortality was not increased in these patients, have reduced the concerns regarding the triple combination.

Exercise tolerance and capacity. The effects of valsartan in addition to usual heart failure therapy on exercise tolerance using the Modified Naughton Protocol were measured in NYHA class II-IV heart failure patients with left ventricular dysfunction (LVEF ≤40%). Increased exercise time from baseline was observed for all treatment groups. Greater mean increases from baseline in exercise time were observed for the valsartan groups compared to the placebo group, although statistical significance was not achieved. The greatest improvements were observed in the subgroup of patients not receiving ACE inhibitor therapy where mean changes in exercise time were two times greater for the valsartan groups compared to the placebo group. The effects of valsartan compared to enalapril on exercise

capacity using the six minute walk test were determined in NYHA class II and III heart failure patients with left ventricular ejection fraction $\leq 45\%$ who had been receiving ACE inhibitor therapy for at least 3 months prior to study entry. Valsartan 80 mg to 160 mg once daily was at least as effective as enalapril 5 mg to 10 mg twice daily, with respect to exercise capacity, as measured by the six minute walk test in patients previously stabilised on ACE inhibitors and directly switched to valsartan or enalapril.

NYHA class, Signs and symptoms, Quality of life, Ejection fraction. In Val-HeFT, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, 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 LVDD 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 were randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor captopril (titrated from 6.25 mg three times daily to highest tolerated dose up to a maximum of 50 mg three times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. 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 at least as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. 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).

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. There was no difference in all-cause mortality based on age, gender, race, baseline therapies or underlying disease.

There was no difference in all-cause mortality or cardiovascular mortality or morbidity when beta-blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of study drug treatment, mortality was higher in the group of patients not treated with a beta-blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial. In addition, the treatment benefits of the combination of valsartan + captopril, valsartan monotherapy, and captopril monotherapy were maintained in patients treated with beta blockers.

5.2 Pharmacokinetic properties

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for Diovan is 23%. Valsartan shows multiexponential decay kinetics ($t_{1/2}$ alpha < 1 hour and $t_{1/2}$ beta about 9 hours).

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan, 70% is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

When Diovan is given with food, the area under the plasma concentration 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. However, this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect, and Diovan can therefore be given either with or without food.

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.

Special populations

Elderly

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to young subjects; and a lower starting dose (40 mg) is recommended for the elderly.

Impaired renal function

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with mild renal impairment (creatinine clearance 20-50 ml/min) limited data are available in patients with moderate-severe

impairment of renal function and a starting dose of 40 mg is recommended for these patients. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment

In a pharmacokinetics trial in patients with mild to moderate hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers.

5.3 Preclinical safety data

In a variety of preclinical safety studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from fetotoxicity in rabbits. Offspring of rats given 600 mg/kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay (see section 4.6 Pregnancy and lactation). The main preclinical safety findings are attributed to the pharmacological action of the compound, and have not been demonstrated to have any clinical significance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity in mice and rats.

6 Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), Macrogol 8000, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172; 40 mg and 160 mg tablets only).

6.2 Special precautions for storage

Do not store above 30°C, store in the original package.

Diovan must be kept out of the reach and sight of children.

6.3 Nature and contents of container

40 mg, 80 mg & 160 mg film-coated tablets are supplied in blister packs.

Manufacturer:

Novartis Pharmaceutica SA, Spain

For Novartis Pharma AG, Switzerland

License Holder:

Novartis Pharma Services AG, 36 Shacham St., Petach-Tikva.