Name of the medicinal product
Diovan®

Description and composition

Active substance
One tablet contains 40 mg, 80 mg or 160 mg valsartan**.**

Pharmaceutical form(s)

Film-coated tablet.

Diovan 40 mg: yellow, ovaloid, scored on one side, slightly convex, with bevelled edges, debossed on one side with DO and with NVR on the other side.

Diovan 80 mg: pale red, round, scored on one side, slightly convex, with bevelled edges, debossed on one side with D/V and NVR on the other side.

Diovan 160 mg: grey-orange, ovaloid, scored on one side, convex, debossed on one side with DX/DX and NVR on the other side.

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 only).

Indications

Hypertension
Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Heart failure
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 (see sections Clinical pharmacology, Pharmacodynamics and Clinical Studies, Heart Failure for details).

Post-myocardial infarction
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 Clinical pharmacology).

Dosage and administration

Dosage

Hypertension
The recommended dose of Diovan is 80 mg film-coated tablet once daily, irrespective of race, age, or gender. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 160 mg, or a diuretic may be added.

Diovan may also be administered with other antihypertensive agents.

Heart failure
The recommended starting dose of Diovan is 40 mg film-coated tablet twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as 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.

Concomitant use with an ACE inhibitor and a beta blocker is not recommended.

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 film-coated tablet 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.

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

NOTE for all indications: No dosage adjustment is required for patients with renal impairment or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

Special populations

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).

Contraindications

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

Pregnancy (see section Women of child-bearing potential (WOCBP), pregnancy, breast-feeding and fertility).

Severe hepatic impairment

Cirrhosis

Biliary obstruction

Concomitant use of angiotensin receptor antagonists (ARBs) - including Diovan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section Interactions, subsection dual blockade of the RAS).

Warnings and precautions

Patients with sodium- and/or volume-depletion

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.

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

Patients with 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.

Patients with impaired renal function

No dosage adjustment is required for patients with renal impairment. However, no data is available for severe cases (creatinine clearance < 10 mL/min.), and caution is therefore advised.

The use of ARBs - including Diovan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section Interactions, subsection dual blockade of the RAS).

Patients with hepatic impairment

Based on pharmacokinetic data, which demonstrate approximately 2-fold increase in plasma concentrations of valsartan in mild to moderate hepatically impaired patients, doses higher than 80 mg daily should only be considered if the clinical benefits, is likely to outweigh the possible risk associated with increased exposure of 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 Diovan therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

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

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia 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.

In patients with heart failure, caution should be observed with the triple combination of an angiotensin-converting enzyme inhibitors, a beta-blocker and an ARB (angiotensin II receptor blocker) (see section Clinical pharmacology).

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 Diovan 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 Interactions, subsection dual blockade of the RAS).

Interactions

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, hyperkalemia, 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 Warnings and precautions).

The concomitant use of ARBs - including Diovan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see section Warnings and precautions).

The concomitant use of ARBs - including Diovan - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section Contraindications).

Potassium: Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, etc.) may lead to increases in serum potassium. If comedication is considered necessary, monitoring of serum potassium is advisable.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors). When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

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

Transporters*:* The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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

As valsartan is not metabolized 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.

Woman of child-bearing potential (WOCBP), pregnancy, breast-feeding and fertility

Woman of child-bearing potential

As for any drug that also acts directly on the RAAS, Diovan should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Pregnancy

As for any drug that also acts directly on the RAAS, Diovan must not be used during pregnancy (see section Contraindications). Due to the mechanism of action of angiotensin II antagonists, a risk 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 newbornrenal dysfunction, when pregnant women have inadvertently taken valsartan. If pregnancy is detected during therapy, Diovan should be discontinued as soon as possible. (see section Non-clinical safety data).

Breast-feeding

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, it is not advisable to use Diovan in breast-feeding mothers.

Fertility

There is no information on the effects of Diovan on human fertility. Studies in rats did not show any effects of valsartan on fertility (see section Non-clinical safety data).

Effects on ability to drive and using machines

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

Adverse drug reactions

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to

< 1/100); rare (≥ 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.

Table-1 Adverse drug reactions in Hypertension

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, Hematocrit decreased, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
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	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Dermatitis bullous, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Blood creatinine increased
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, edema, 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:

Table-2 Post-myocardial infarction and/or heart failure

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	Blood potassium increased
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	Liver function test abnormal
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Rash, Pruritis, dermatitis bullous
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Blood creatinine increased
Not known	Blood Urea increased
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, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Overdosage

Overdose 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.

Clinical pharmacology

Pharmacotherapeutic group, ATC:

Angiotensin II antagonists, plain, ATC code: C09C A03.

Pharmacodynamics (PD)

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 AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 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 (2.6% 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.

Pharmacokinetics (PK) properties

Absorption

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. When valsartan 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. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

Steady-state volume of distribution of valsartan after intravenous administration is about 17 liters low (about 17 L), indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum album.

Biotransformation

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multiexponential decay kinetics (t½α <1 h and t½ß about 9 h). 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 feces and 30% in the urine, mainly as unchanged compound. Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 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.

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.

Clinical studies

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

Hemodynamics and Neurohormones. 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 Val-HeFT study, plasma norepinephrine and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Morbidity and mortality. Val-HeFT was a randomized, 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 randomized 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, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. 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 hospitalization. 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. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

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 2 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 ≤ 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 stabilized 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 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 randomized, 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 were randomized 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.

Non-clinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and Long term toxicity

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans. In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Reproductive toxicity

In embryofetal development studies (Segment II) in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of ≥200 mg/kg/day and in rabbits at doses of ≥ 10 mg/kg/day. In a peri- and postnatal development toxicity (segment III) study, the 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 WOCBP, pregnancy, breast-feeding and fertility). The main preclinical safety findings are attributed to the pharmacological action of the compound, and have not been demonstrated to have any clinical significance.

Mutagenicity
Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard in vitro and in vivo genotoxicity studies.

Carcinogenicity
There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

Pharmaceutical information

Incompatibilities
Not applicable.

Special precautions for storage
Do not store above 30°C, store in the original package.
DIOVAN should not be used after the date marked "EXP" on the pack.
Diovan should be kept out of reach of children.
Shelf life: The expiry date is indicated on the packaging.

Nature and contents of container
Alu Alu blister packs

Instructions for use and handling
No special requirements.

HARUS DENGAN RESEP DOKTER

Package

Blister

Diovan® 40 mg : Box of 2 blisters @ 14 film coated tablets	Reg No: DKI2197301217A1
Diovan® 80 mg : Box of 2 blisters @ 14 film coated tablets	Reg No: DKI2197301217B1
Diovan® 160 mg : Box of 2 blisters @ 14 film coated tablets	Reg No: DKI2197301217C1

Manufactured by Siegfried Barberá S.L., Barberà del Vallès, Barcelona, Spain for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Strip

Diovan® 80 mg : Box of 3 strips @ 10 film coated tablets	Reg No: DKL1930413017A1
Diovan® 160 mg : Box of 3 strips @ 10 film coated tablets	Reg No: DKL1930413017B1

Manufactured by Siegfried Barberá S.L., Barberà del Vallès, Barcelona, Spain for Novartis Pharma AG, Basel, Switzerland.

Imported and packaged by PT Novartis Indonesia, Jakarta, Indonesia.

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