NOVARTIS

TRADE NAME

Diovan® 80 mg and 160 mg film coated tablets

DESCRIPTION AND COMPOSITION

Active substance

One tablet contains 80 mg or 160 mg of valsartan**.**

Pharmaceutical Forms

Film-coated tablet (FCT)

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, scored on one side; with debossing "DX/DX" on the scored side and "NVR" on the other side

Appearance of tablets may differ between countries. Certain dosage strengths may not be available in all countries.

The score line on one side of Diovan 80mg or 160mg FCT is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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; 160 mg tablets only),

Pharmaceutical formulations may vary between countries.

INDICATIONS

Hypertension

Treatment of hypertension.

Heart failure

Treatment of heart failure (NYHA class II-IV) in patients receiving standard therapy such as diuretics, digitalis and either angiotensin-converting enzyme (ACE) inhibitors or beta-blockers but not both; presence of all these standard therapies is not mandatory.

Diovan improves morbidity in these patients, primarily via reduction in hospitalization for heart failure. Diovan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see section CLINICAL PHARMACOLOGY).

Post-myocardial infarction

Diovan is indicated to improve survival following recent 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 REGIMEN AND ADMINISTRATION

Dosage regimen

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 160mg. 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. Up-titration 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 160mg 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 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 impairment of non-biliary origin and without cholestasis.

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).

Method of administration

Film-coated tablets: Diovan may be taken independently of a meal and should be administered with water.

CONTRAINDICATIONS

Severe hepatic impairment, cirrhosis, biliary obstruction

Severe renal impairment (creatinine clearance < 10mL/min) and patients undergoing dialysis.

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

Pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)

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)

The concomitant use of Diovan with aliskiren-containing products is contraindicated in patients with renal impairment (GFR <60 mL/min/1.73m^2) (see INTERACTIONS).

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.

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

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous (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 hemodynamics, 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.

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.

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

No dosage adjustment is required for patients with hepatic impairment. Valsartan is mostly eliminated unchanged in the bile, and patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders showed lower valsartan clearance (see section CLINICAL PHARMACOLOGY).

Patients with severe hepatic impairment, cirrhosis, biliary obstruction are contraindicated from using Diovan (see section CONTRAINDICATIONS).

Patients with 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 REGIMEN AND 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 ACEIs or ARBs 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.

In patients with heart failure, concomitant use of Diovan, an ACEI and a beta blocker is not recommended (see section CLINICAL PHARMACOLOGY). In the Valsartan Heart Failure Trial (Val-HeFT), this triple combination was associated with an unfavourable heart failure outcome. In the VALsartan In Acute myocardial iNfarcTion trial (VALIANT), the combination of Diovan with the ACEI captopril did not add further benefit over captoril alone, therefore this combination is not recommended.

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 ACEIs. 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)

There is evidence that the concomitant use of ACEIs, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAS through the combined use of ACEIs, ARBs or aliskiren is therefore not

recommended (see INTERACTIONS).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACEIs and ARBs should not be used concomitantly in patients with diabetic nephropathy.

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 in table 1 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.

Hypertension

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, Ddermatitis 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.

Heart failure and/ or post-myocardial infarction

The safety profile seen in controlled-clinical studies in patients with heart failure and/ or post-myocardial infarction varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in heart failure and/ or post-myocardial infarction patients are listed below in table 2:

Table 2 Adverse drug reactions in heart failure and/or post-myocardial infarction

Blood and lymphatic system disorder	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia[#]
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	Dermatitis bullous, rash, pruritis
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

Blood potassium increased (frequency unknown)- reported in post market reporting.

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.

The following serious adverse events, irrespective of causality and with unknown frequency, have been reported from clinical studies or post-marketing experiences: Toxic epidermal necrolysis (TEN), Stevens-Johnsons syndrome (SJS), erythema multiforme (EM), toxic skin eruption, skin necrosis, exfoliative rash, pemphigus and pemphigoid.

INTERACTIONS

Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren
Clinical trial data has shown that dual blockade of the RAS through the combined use of ACEIs, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see section CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). 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 and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When ARBs 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 ARBs and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure. 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 ACEIs or ARBs, 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 (e.g., 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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

As for any drug that 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 newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

If pregnancy is detected during therapy, Diovan should be discontinued as soon as possible. (see section ANIMAL DATA).

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.

Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

Animal data

In embroyofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600mg/kg/day approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320mg/day and a 60-kg patient) and in rabbits at doses of 10mg/kg/day approximately 0.6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320mg/day and a 60-kg patient). There was no evidence of maternal toxicity or fetotoxicity in mice up to dose level of 600mg/kg/day approximately 9 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320mg/day and a 60-kg patient).

Lactation

Risk Summary

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

Females and males of reproductive potential

As for any drug that 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.

Infertility

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 USE MACHINES

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur.

OVERDOSAGE

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 hemodialysis.

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 ($P < 0.05$) 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.

Pharmacokinetics (PK)

Absorption

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 Diovan can therefore be given either with or without food.

Distribution

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

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). 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.

Special populations

Geriatric patients (aged 65 years or above)

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to young subjects; however, this has not been shown to have any clinical

significance.

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 renal impairment. 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

About 70% of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation, and, as expected, systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic impairment of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction (see section WARNINGS AND PRECAUTIONS).

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 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 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.

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 ≤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 dyspnoea, fatigue, edema 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, hospitalization 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/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, 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/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen 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

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, approximately 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320mg/day and a 60-kg patient).

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

See folding box.

Diovan should not be used after the date marked “EXP” on the pack.
Diovan must be kept out of the reach and sight of children.

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