Diovan®

Composition

Active substance: Valsartan

Excipients:

Film-coated tablets: 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, 160 mg and 320 mg tablets only), brown iron oxide (mixture of red iron oxide and black iron oxide (320 mg tablets only).

oral solution: Sucrose, Methyl parahydroxybenzoate (E218), Potassium sorbate, Poloxamer (188), Citric acid, anhydrous, Sodium citrate, Artificial blueberry flavour (538926 C), Propylene glycol (E1520), Sodium hydroxide, Hydrochloric acid, Purified water .

Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

Diovan 40

Film-coated tablets containing 40 mg valsartan

Yellow, ovaloid, slightly convex film-coated tablet, scored on one side. Imprinted with DO on one side and NVR on the other side.

Diovan 80

Film-coated tablets containing 80 mg valsartan

Pale red, round, slightly convex film-coated tablets, scored on one side. Imprinted with D/V on one side and NVR on the other side.

Diovan 160

Film-coated tablets containing 160 mg valsartan

Grey-orange, ovaloid, convex film-coated tablets, scored on one side. Imprinted with DX/DX on one side and NVR on the other side.

Diovan 320

Film-coated tablets containing 320 mg valsartan

Dark grey-violet, ovaloid, slightly convex film-coated tablets. Imprinted with DXL on one side and NVR on the other side.

Diovan

Oral solution containing 3 mg/ml Valsartan

Clear, colourless to pale yellow solution. Each ml solution contains 3 mg of valsartan.

Indications/Potential uses

Essential hypertension

Treatment of mild and moderate essential hypertension in adults and in children and adolescents 6-18 years of age.

Heart failure

Mild to moderate heart failure (NYHA class II and III) in adults, normally in combination with diuretics and digitalis, in cases where treatment with ACE inhibitors is unsuitable due to adverse effects specifically attributable to ACE inhibitors (cough). Adverse effects resulting from the general influence of ACE inhibitor therapy on the renin-angiotensin-aldosterone system (e.g. progressive renal failure, hyperkalaemia) do not constitute an indication for Diovan.

Post-myocardial infarction

Long-term prophylaxis in adult patients with stable status following myocardial infarction associated with left-ventricular dysfunction and ejection fraction ≤ 40%.

Dosage/Administration

Usual dosage recommendations

Essential hypertension

The recommended dose of Diovan is 80 mg or 160 mg once daily, irrespective of race, age or gender.

A substantial antihypertensive effect is attained within 2 weeks, and the maximum antihypertensive effect is seen after 4 weeks of commencing treatment. If the reduction in blood pressure is insufficient, the daily dose may be increased to 160 mg or up to a maximum of 320 mg as a film-coated tablet, or a diuretic may be added.

Diovan may be administered with other antihypertensive agents.

Heart failure

The recommended starting dose of valsartan is 40 mg as a film-coated tablet twice daily (corresponds to half an 80 mg film-coated tablet twice daily). Depending on tolerability, the dose should be increased gradually, first to 80 mg valsartan twice daily, then to 160 mg valsartan twice daily as a film-coated tablet. If a diuretic is administered concomitantly, consideration should be given to reducing the dose of the diuretic. In clinical trials, the maximum daily dose was 320 mg valsartan (160 mg valsartan twice daily).

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

Post-acute myocardial infarction

Therapy with Diovan may be initiated as early as 12 hours after acute myocardial infarction. After an initial dose of 20 mg twice daily, the dose should be increased gradually (generally over the course of a few weeks) to 40 mg, 80 mg and 160 mg twice daily as a film-coated tablet. The starting dose can be achieved using the 40 mg divisible film-coated tablet.

The target maximum dose is 160 mg twice daily. In general, depending on individual

tolerability during dose titration, it is recommended that patients reach a dose level of 80 mg twice daily by two weeks after treatment initiation, and that the target maximum dose be achieved after three months.

If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction.

Diovan may be given concomitantly with other post-acute myocardial infarction therapies, e.g. thrombolytic agents, acetylsalicylic acid, beta-blockers or statins.

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

Special dosage recommendations

Renal and hepatic impairment

NOTE for all indications: No dosage adjustment is required for patients with mild to moderate renal impairment.

In patients with hepatic impairment, the daily dose should not exceed 80 mg valsartan.

Paediatric population (hypertension in children and adolescents)

Children and adolescents 6-18 years of age

Film-coated tablets

The initial dose is one 40 mg film-coated tablet once daily for children weighing below 35 kg, and 80 mg once daily for children and adolescents weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials, please refer to the table below. Doses higher than those listed have not been studied and are therefore not recommended.

Body weight	**Maximum dose studied in clinical trials**
≥ 18 kg to < 35 kg	80 mg
≥ 35 kg to < 80 kg	160 mg
≥ 80 kg to ≤ 160 kg	320 mg

Oral solution

For children and adolescents who are unable to swallow film-coated tablets, the use of Diovan oral solution is recommended. Systemic exposure and peak plasma concentration with the oral solution are 1.7 times and 2.2 times higher, respectively, than the values obtained after taking the film-coated tablets.

The initial dose of Diovan oral solution is 20 mg once daily (corresponding to 7 ml of the solution) for children and adolescents weighing below 35 kg, and 40 mg once daily (corresponding to 13 ml of the solution) for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response up to a maximum dose of 40 mg valsartan once daily (corresponding to 13 ml of the solution) for children and adolescents weighing below 35 kg, and

80 mg valsartan once daily (corresponding to 27 ml of the solution) for children and adolescents weighing 35 kg or more.

It is not recommended to switch between Diovan film-coated tablets and Diovan oral solution unless clinically required. If switching from Diovan film-coated tablets to Diovan oral solution is considered necessary on clinical grounds, the valsartan dose should be adjusted as described in the table below, and blood pressure should be carefully monitored. The dose should be titrated based on blood pressure response and tolerability.

Film-coated tablets	**Oral solution**	
Valsartan dose	Valsartan dose to administer when switching	Volume to take
40 mg	20 mg	7 ml
80 mg	40 mg	13 ml
160 mg	80 mg	27 ml
320 mg	Due to the high volume of solution that would be necessary, use of the solution is not recommended.	Not applicable

If switching from Diovan oral solution to Diovan film-coated tablets is considered clinically essential, initially the same dose in milligrams should be given. Subsequently, frequent blood pressure monitoring should be performed, taking into account potential under-dosing, and the dose should be titrated further based on blood pressure response and tolerability.

Use in children under 6 years of age

Available data are described in the sections "Adverse effects", "Pharmacodynamics" and "Pharmacokinetics". However, the safety and efficacy of Diovan in children aged 1 to 6 years have not been established.

Children and adolescents with heart failure and recent myocardial infarction

Diovan is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

Film-coated tablets: Diovan can be taken with or without food, and should be administered with water.

Oral solution: Diovan can be taken with or without food (see "Pharmacokinetics - Absorption"). It is recommended that Diovan be taken at the same time every day, e.g. in the morning for hypertension, and mornings and evenings for heart failure or post-myocardial infarction.

Contraindications

Hypersensitivity to valsartan or to any of the excipients of Diovan.

Pregnancy and breastfeeding (see "Pregnancy/Breastfeeding").

There are no data on patients with severe renal impairment (creatinine clearance < 10 ml/minute).

Diovan is contraindicated in patients with hereditary angioedema, or in those who have developed angioedema during previous treatment with an ACE inhibitor or angiotensin II receptor antagonist.

Concomitant use of angiotensin receptor antagonists (ARBs) – including Diovan – or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus (Type I and Type 2) and patients with renal impairment (GFR <60 ml/min) (see "Interactions", subsection entitled "Dual blockade of the RAS").

Warnings and precautions

Sodium and/or volume-depleted patients

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Diovan. Sodium and/or volume depletion should be corrected before starting treatment with Diovan, or the dose of existing diuretic therapy reduced.

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

Renal artery stenosis

Short-term (4-day) administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with unilateral or bilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment.

The concomitant use of ARBs – including Diovan – or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR <60 ml/min) (see "Interactions", subsection entitled "Dual blockade of the RAS").

In the VALIANT study, hypotension and renal impairment were more frequent with valsartan than with captopril. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of those treated with valsartan, 4.8% of those treated with the combination of valsartan and captopril, and 3.4% of those treated with captopril.

Hepatic impairment

In patients with hepatic impairment, the daily dose should not exceed 80 mg valsartan. Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see "Pharmacokinetics"). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders.

Heart failure/Post-acute myocardial infarction

Use of Diovan in patients with heart failure or post-acute myocardial infarction may generally result in a reduction in blood pressure. Discontinuation of Diovan due to persistent symptomatic hypotension is not usually necessary, provided the dosing instructions are followed. Caution is required, particularly at the start of therapy, in patients with heart failure or post-acute myocardial infarction (see "Dosage/Administration").

Due to inhibition of the RAAS, changes in renal function should be anticipated in predisposed patients. In patients with severe heart failure whose renal function depends on the activity of the RAAS, treatment with ACE inhibitors and angiotensin II receptor antagonists has been associated with oliguria and/or progressive azotaemia, and (rarely) with acute renal failure and/or death. Monitoring of patients with heart failure or post-acute myocardial infarction should always include assessment of renal function.

Heart failure

Particular caution is required with the triple combination of an ACE inhibitor, a beta-blocker and valsartan in heart failure patients, as heart failure-related morbidity and mortality is increased with concomitant administration of beta-blockers and ACE inhibitors compared to placebo.

There have been no studies of the safety and efficacy of Diovan in children.

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 must be immediately discontinued in patients who develop angioedema, and Diovan must not be re-administered.

Dual blockade of the renin-angiotensin system (RAS)

It is not recommended to co-administer ARBs, including Diovan, with other agents blocking the RAS such as ACEIs or aliskiren. In certain patients, this combination is contraindicated (see "Contraindications", "Interactions", subsection entitled "Dual blockade of the RAS").

Fertility

There is no information on the effects of valsartan on human fertility. Studies in rats did not show any effects of valsartan on fertility (see "Preclinical data").

Paediatric population

Renal impairment

Use in paediatric patients with a glomerular filtration rate <30 ml/min/1.73 m^2 and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a glomerular filtration rate >30 ml/min/1.73 m^2 (see "Pharmacokinetics"). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) that may impair renal function.

Hepatic impairment

As in adults, particular caution should be exercised when administering valsartan to paediatric patients with obstructive cholestasis (see "Pharmacokinetics"). There is limited clinical experience with Diovan in paediatric patients with mild to moderate hepatic impairment.

Special excipients (Diovan oral solution)

Diovan oral solution contains 0.3 g sucrose per ml. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Diovan oral solution as it contains sucrose.

Diovan oral solution contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Diovan oral solution contains poloxamer (188), which may cause softened stools.

Switching dosage forms

Diovan oral solution is not bioequivalent to the film-coated tablet formulation, and patients should not be switched unless clinically essential. For dosing recommendations in this case, see "Dosage/Administration".

Interactions

There is no experience with concomitant use of valsartan and lithium. Regular monitoring of serum lithium concentrations is therefore recommended during concurrent use of lithium and Diovan.

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 renal disorders (including acute renal failure) compared to monotherapy. It is recommended to regularly monitor blood pressure, renal function and electrolytes in patients receiving Diovan and other agents that affect the RAS (see "Warnings and precautions").

The concomitant use of ARBs – including Diovan – or of ACEIs with aliskiren, is contraindicated in patients with severe renal impairment (GFR <60 ml/min) (see "Warnings and precautions" and "Contraindications").

The concomitant use of ARBs – including Diovan – or of ACEIs with aliskiren, is contraindicated in patients with Type 1 and Type 2 diabetes (see "Contraindications").

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 be increased further.
Potassium: 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. Caution is therefore necessary when such co-medication is given.
Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX2) inhibitors: Concomitant administration of NSAIDs and COX2 inhibitors may attenuate the antihypertensive effect of angiotensin II receptor antagonists (ARBs). In patients who are elderly, volume depleted (including those on diuretic therapy), or have compromised renal function, co-administration of NSAIDs (or COX2 inhibitors) with an ARB may increase the risk of worsening of renal function, including possible acute renal failure. These drugs should therefore be combined in such patients only with caution and monitoring of renal function.
Paediatric patients
In hypertension in children and adolescents 6-18 years of age, in whom underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system and may increase serum potassium. Renal function and serum potassium should be closely monitored in these patients.
Transporters: In vitro studies 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 transporters OATP1B1 (rifampin, ciclosporin) or MRP2 (ritonavir) may therefore increase systemic exposure to valsartan.
No drug interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

Pregnancy/Breastfeeding

Pregnancy
As Diovan acts directly on the RAAS, it must not be taken during pregnancy or by women who are planning to become pregnant (see "Contraindications").
Due to the mechanism of action of angiotensin II receptor antagonists, embryonic and fetal risk cannot be excluded. In retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. In addition, fetal injury and death have been reported in association with the use during the second and third trimesters of drugs that directly act on the renin-angiotensin-aldosterone system (RAAS). In humans, fetal renal perfusion,

which is dependent on the development of the RAAS, begins during the second trimester. The risks associated with Diovan treatment are therefore higher during the second and third trimesters. There have been reports of spontaneous abortion, oligohydramnios and neonatal renal dysfunction when pregnant women have inadvertently taken valsartan.
All neonates exposed to the drug *in utero* should be carefully checked for adequate urine output, hyperkalaemia and blood pressure. If necessary, appropriate medical steps (e.g. rehydration) must be taken to remove the drug from the circulation.
If pregnancy is detected during therapy, Diovan must be discontinued.
Breastfeeding
Valsartan was excreted in the milk of lactating rats. There have been no studies in breastfeeding women and Diovan should therefore not be used in breastfeeding women.

Effects on ability to drive and use machines

Like other antihypertensive agents, Diovan may impair reactions, ability to drive and ability to use tools and machines. Caution is recommended.

Adverse effects

Hypertension/heart failure/myocardial infarction
Adverse events observed more frequently with valsartan than placebo in clinical trials, and those originating from individual reports, are listed by system organ class.
For *very rare*, *rare* and *uncommon* adverse effects not detectable in clinical trials with adults, a cumulative search was performed in the safety database.
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).
Infections and infestations
Common: Viral infections.
Uncommon: Upper respiratory tract infection, pharyngitis, sinusitis.
Very rare: Rhinitis.
Blood and lymphatic system disorders
Uncommon: Neutropenia.
Very rare: Thrombocytopenia.
Immune system disorders
Very rare: Hypersensitivity reactions, including serum sickness.
Metabolism and nutrition disorders
Uncommon: Hyperkalaemia*[#].
Psychiatric disorders
Uncommon: Insomnia, libido decrease.
Nervous system disorders

Common: Postural dizziness[#].

Uncommon: Syncope*.

Rare: Dizziness[##].

Very rare: Headache[##].

Ear and labyrinth disorders

Uncommon: Vertigo.

Cardiac disorders

Uncommon: Heart failure*.

Very rare: Cardiac arrhythmias.

Vascular disorders

Common: Orthostatic hypotension[#].

Uncommon: Hypotension*[##].

Very rare: Vasculitis.

Respiratory disorders

Uncommon: Cough.

Gastrointestinal disorders

Uncommon: Diarrhoea, abdominal pain.

Very rare: Nausea[##], vomiting.

Skin and subcutaneous tissue disorders

Very rare: Angioedema**, exanthema, pruritus, rash.

Not known: Bullous dermatitis.

Musculoskeletal disorders

Uncommon: Back pain.

Very rare: Arthralgia, myalgia.

Renal and urinary disorders

Very rare: Renal failure**[##], acute renal failure**, renal impairment**.

Pregnancy and perinatal conditions

Very rare: Fetal complications.

General disorders

Uncommon: Fatigue, asthenia, oedema.

Laboratory findings

Common: Elevation of serum creatinine, increase in blood urea.

Very rare: Increase in serum bilirubin, decrease in blood haemoglobin/haematocrit, abnormal liver function values.

* reported in post-myocardial infarction

[#] reported in heart failure

** uncommonly reported in post-myocardial infarction

[##] reported more frequently in heart failure (*common*: dizziness, renal impairment, hypotension; *uncommon*: headache, nausea)

Laboratory findings

In rare cases, valsartan therapy may be associated with a reduction in haemoglobin and haematocrit. In controlled clinical trials, significant (> 20%) reductions in haematocrit and haemoglobin were reported, respectively, in 0.8% and 0.4% of patients receiving Diovan. In contrast, 0.1% of patients receiving placebo showed a reduction in levels of haematocrit or haemoglobin.

In controlled clinical trials, neutropenia was observed in 1.9% of patients treated with valsartan and 1.6% of patients treated with an ACE inhibitor.

In controlled clinical trials in patients with essential hypertension, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0.8%, 4.4% and 6% of patients treated with valsartan, and 1.6%, 6.4% and 12.9% of patients treated with an ACE inhibitor.

There were uncommon reports of elevated liver function values in patients treated with valsartan.

No special monitoring of laboratory parameters is necessary in patients with essential hypertension receiving valsartan therapy.

In heart failure patients, increases of more than 50% in serum creatinine were observed in 3.9% of valsartan-treated patients, compared with 0.9% of patients given placebo. Increases of more than 20% in serum potassium were observed in 10% of valsartan-treated patients, compared with 5.1% of patients given placebo.

In heart failure patients, increases of more than 50% in blood urea were observed in 16.6% of valsartan-treated patients, compared with 6.3% of patients given placebo.

In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of those treated with valsartan, 4.8% of those treated with the combination of valsartan and captopril, and 3.4% of those treated with captopril.

At 5.8%, discontinuations due to adverse effects were lower in the group treated with valsartan than in the group treated with captopril (7.7%).

Paediatric population (hypertension)

The antihypertensive effect of valsartan has been evaluated in two randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. No relevant differences in terms of type, frequency and severity of adverse effects were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients. Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with Diovan for up to one year.

In a double-blind, randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminase

elevations were observed. In a second study in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a one-year open-label extension. These cases occurred in a patient population with significant comorbidities. A causal relationship to Diovan has not been established.

Overdose

Overdose with Diovan may result in marked hypotension, which may lead to a depressed level of consciousness, circulatory collapse and/or shock. If ingestion is recent, vomiting should be induced. Otherwise, the usual treatment is i.v. infusion of normal saline solution.
Valsartan is unlikely to be removed by haemodialysis.

Properties/Actions

ATC code: C09CA03

Mechanism of action/Pharmacodynamics

The active hormone of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through angiotensin-converting enzyme (ACE). Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor effect. In addition, it promotes sodium retention and stimulates aldosterone secretion.
Valsartan is an orally active and specific angiotensin (AT) 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 angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptors, which appears to further counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has about 20,000-fold greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan does not inhibit ACE (= kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin. Angiotensin II antagonists are unlikely to cause cough since they have no effect on ACE and do not potentiate bradykinin or substance P. In clinical trials comparing valsartan 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%). In a clinical trial involving patients with a history of dry cough during ACE inhibitor therapy, 19.5% of patients 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 affect other hormone receptors or ion channels known to be important in cardiovascular regulation.

Clinical efficacy

Hypertension

Valsartan reduces blood pressure in patients with hypertension without affecting pulse rate.
In most patients, onset of antihypertensive effect occurs within 2 hours after administration of a single oral dose, and the peak reduction of blood pressure is achieved after 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. The maximum reduction in blood pressure is generally attained 2-4 weeks after the start of treatment and is sustained during long-term therapy. Concomitant administration of hydrochlorothiazide results in a significant additional reduction in blood pressure.
Withdrawal of valsartan does not bring about rebound hypertension or other adverse effects.
Valsartan does not alter fasting levels of total cholesterol, triglycerides, serum glucose or uric acid in hypertensive patients.
Heart failure
Haemodynamics and neurohormones: A haemodynamic study in 116 patients (36.3% of whom in NYHA class II, 46% in NYHA class III and 17.7% in NYHA class IV) included only patients untreated with ACE inhibitors for at least 6 months prior to enrolment. In this study, valsartan significantly lowered pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR) and systolic blood pressure (SBP), and increased cardiac output (CO) 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.
Clinical trial: Val-HeFT (Valsartan Heart Failure Trial) was a multinational, double-blind clinical trial in 5,010 patients with NYHA class II (62%) to IV (2%) heart failure with a left ventricular ejection fraction (LVEF) < 40%. Baseline therapy was chosen by the attending physician, and the patients were randomized to receive either placebo or valsartan, which was titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily. 181 patients given placebo and 185 given valsartan were not receiving concomitant ACE inhibitor therapy. The mean duration of follow-up was around two years. The study had two primary endpoints, both assessed by time to first event: all-cause mortality, and heart failure-related morbidity. The latter was defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more.
Valsartan reduced heart failure-related morbidity in the subgroup of 7% of patients not receiving an ACE inhibitor, but not in the group receiving concomitant ACE inhibitor therapy. The following data relate to the subgroup not receiving an ACE inhibitor.

	Placebo (n = 181)	Valsartan (n = 185)	Relative risk (95% CI)
Heart failure-related morbidity (%)	77 (42.5%)	46 (24.9%)	0.51 (0.35-0.73)
Percentage of heart failure-related morbidity cases			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37-0.91)
Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04-5.20)
Treatment for manifest heart failure	1 (0.6%)	0 (0.0%)	-
Hospitalization for heart failure	48 (26.5%)	24 (13.0%)	0.43 (0.27-0.71)
Cardiovascular mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40-1.05)
Non-fatal morbidity	49 (27.1%)	24 (13.0%)	0.42 (0.26-0.69)

Patients given valsartan showed an increase in ejection fraction and a reduction in left ventricular internal diastolic diameter (LVIDD), as compared with those given placebo. Effects were generally consistent across age and gender-defined subgroups. The number of black patients was too small to permit a meaningful assessment of this subgroup.

Post-myocardial infarction

The VALIANT (Valsartan In Acute Myocardial Infarction) trial was a randomized, controlled, multinational, double-blind clinical study in 14,703 patients with acute myocardial infarction and symptomatic or radiological evidence of left-ventricular failure and/or left-ventricular systolic dysfunction (manifested as 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 (initial dose 20 mg twice daily, titrated gradually to the highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor captopril (initial dose 6.25 mg three times daily, titrated gradually to the 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 starting dose of valsartan was 20 mg twice daily, which was increased to the highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The mean observation period 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 and 94% Caucasian; 53% were 65 years of age or older. The primary endpoint was all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in all three treatment groups: valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%). Combining valsartan with captopril did

not result in any additional benefit over captopril as monotherapy. There were no differences based on age, gender, race, baseline therapy or co-morbidity. Valsartan was effective both in prolonging the time to, and reducing, cardiovascular mortality, hospitalization for heart failure, recurrent myocardial infarction, resuscitation following cardiac arrest, and non-fatal myocardial infarction (secondary composite endpoint).

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

Paediatric population (hypertension)

The antihypertensive effect of valsartan has been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age, and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

Clinical experience in children at or above 6 years of age

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg valsartan film-coated tablets daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80 or 160 mg valsartan film-coated tablets daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10 or 12 mmHg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at the end of the dosing interval was 4 and 7 mmHg lower than in patients who received placebo. In patients receiving the low dose of valsartan, systolic blood pressure at the end of the dosing interval was similar to that of patients who received placebo. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril film-coated tablets for 12 weeks. Patients weighing between ≥18 kg and <35 kg received 80 mg valsartan or 10 mg enalapril; those between ≥35 kg and <80 kg received 160 mg valsartan or 20 mg enalapril; those ≥80 kg received 320 mg valsartan or 40 mg enalapril. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mmHg) (non-

inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children under 6 years of age

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response relationship could not be demonstrated. In the second study, higher doses of valsartan were associated with greater blood pressure reductions, but the dose-response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see "Adverse effects").

Pharmacokinetics

Absorption

Following oral administration of valsartan, the peak plasma concentration (C_{max}) is reached within 2–4 hours. The mean absolute bioavailability of valsartan is 23% (range 23 ± 7). Its pharmacokinetics are linear in the dose range studied. When given once daily, valsartan shows little accumulation. Plasma concentrations were similar in men and women.

When valsartan is given with food, the area under the plasma concentration curve (AUC) is reduced by 48%, and C_{max} by 59%, although from eight hours post dosing, plasma valsartan concentrations are similar for ingestion with or without food. The reductions in AUC and C_{max} do not result in a clinically significant reduction in therapeutic effect, and Diovan can therefore be taken without regard to meals.

Distribution

Valsartan is extensively bound to serum proteins (94-97%), mainly serum albumin. Steady state is reached within 1 week. The steady-state volume of distribution after intravenous administration is about 17 litres, indicating that valsartan is not distributed into tissues extensively. Plasma clearance is relatively slow (about 2 litres/hour), compared with hepatic blood flow (about 30 litres/hour).

Biotransformation

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

Elimination

Valsartan shows multiexponential decay kinetics (primary (alpha) half-life < 1 hour, terminal (beta) half-life about 9 hours).

Of the absorbed dose of valsartan, approximately 83% is excreted in the faeces and 13% in the urine, mainly as unchanged compound.

Following intravenous administration, plasma clearance is about 2 litres/hour and renal clearance about 0.62 litres/hour (about 30% of total clearance). The half-life of valsartan is 6 hours.

Pharmacokinetics in special patient populations

Elderly patients

A somewhat higher systemic availability of valsartan was observed in some elderly patients (> 65 years) compared to younger volunteers, but this was not found to be clinically relevant.

Renal impairment

As may be expected for a compound with renal clearance accounting for only 30% of total plasma clearance, no correlation was found between renal function and systemic availability of valsartan. Dose adjustment is therefore not required in patients with renal impairment (for severe renal impairment, see "Contraindications"). No studies have been performed in dialysis patients. However, as valsartan is highly bound to plasma proteins, it 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 may be expected, there is no correlation between systemic availability of valsartan and the degree of hepatic dysfunction. Dose adjustment is therefore not necessary in patients with hepatic impairment of non-biliary origin and without cholestasis. The AUC of valsartan was approximately doubled in patients with biliary cirrhosis or biliary obstruction (see "Warnings and precautions").

Heart failure patients

The time to peak plasma 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 litres/hour. Age does not affect the apparent clearance in heart failure patients.

Paediatric population

In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/hour/kg) of valsartan was comparable across the age range of 1 to 16 years and comparable to that of adults receiving the same formulation. See "Warnings and precautions - *Paediatric population*".

Preclinical 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.

Valsartan tested negatively for mutagenicity, clastogenicity, effects on reproductive performance and carcinogenicity.
In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) in rats caused a reduction in red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and 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 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 that 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, hypertrophy of the renal juxtaglomerular cells does not seem to be relevant. 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.
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 "Pregnancy/Breastfeeding"). The main preclinical safety findings are attributable 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 or rats.
Paediatric population
Daily oral dosing of neonatal/juvenile rats (from postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on a systemic exposure basis) produced persistent, irreversible kidney damage. These effects mentioned above represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period corresponds to 36 weeks of pregnancy in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (4-6 weeks postnatal) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate safety problems for children older than 1 year.

Other information

Special precautions for storage
Diovan film-coated tablets: Protect from moisture and do not store above 30°C.

Diovan oral solution: Do not store above 30°C. Once opened, the bottle can be stored for up to 3 months.
Keep out of the reach of children.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box

Information last revised

April 2014

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists