

Diovan®**valsartan****Capsules****Rx only****Prescribing Information****USE IN PREGNANCY**

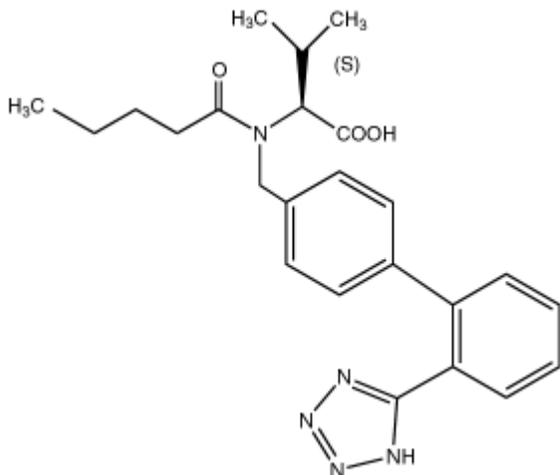
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.

See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

Diovan® (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine. Its empirical formula is C₂₄H₂₉N₅O₃, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as capsules for oral administration, containing either 80 mg or 160 mg of valsartan.

The inactive ingredients of the capsules are cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT₁ receptor than for the AT₂ receptor. The increased plasma levels of angiotensin II following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT₁ receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10%-35%).

Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

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).

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L),

indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations

Pediatric: The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics and Clinical Effects

Hypertension

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Diovan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of

response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF <40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4

mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the table below.

	Placebo N=2499	Valsartan N=2511	Hazard ratio (95% CI)	Nominal p-value
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.80
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE inhibitor		With ACE inhibitor	
	Placebo (N=181)	Valsartan (N=185)	Placebo (N=2318)	Valsartan (N=2326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo N=181	Valsartan N=185	Hazard ratio (95% CI)
Components of HF morbidity			
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)
CHF therapy	1 (0.6%)	0 (0.0%)	---
CHF hospitalization	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)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Concomitant use of an ACE inhibitor, a beta-blocker, and valsartan was associated with a worse outcome for heart failure morbidity, as shown in the following table.

	Placebo (N=816)	Valsartan (N=794)	Hazard ratio (95% CI)
Heart failure morbidity	179 (21.9%)	202 (25.4%)	1.18 (0.97, 1.45)
All-cause mortality	97 (11.9%)	129 (16.2%)	1.42 (1.09, 1.85)

It is not known if this is a reproducible effect or a chance occurrence. The use of a beta-blocker did not appear to influence the effect of valsartan in patients not receiving an ACE inhibitor.

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

INDICATIONS AND USAGE

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 CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure for details.)

CONTRAINDICATIONS

Diovan® (valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan® (valsartan) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess

the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension in valsartan treated patients was 5.5% compared to 1.8% in placebo treated patients.

PRECAUTIONS

General

Impaired Hepatic Function: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan® (valsartan) to these patients.

Impaired Renal Function - Hypertension: In studies of ACE inhibitors in hypertensive patients with

unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Impaired Renal Function – Heart Failure: 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. Similar outcomes have been reported with Diovan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). Evaluation of patients with heart failure should always include assessment of renal function.

Concomitant Therapy in Patients with Heart Failure: In patients with heart failure, concomitant use of Diovan, an ACE inhibitor, and a beta blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable heart failure outcome (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure).

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (eg. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m² basis.

(Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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.)

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In the controlled clinical trials of valsartan, 1214 (36.2%) of hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.

ADVERSE REACTIONS

Hypertension

Diovan® (valsartan) has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients

treated with Diovan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole: Allergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipation, dry mouth, dyspepsia, and flatulence

Musculoskeletal: Back pain, muscle cramps, and myalgia

Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Heart Failure

The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2506) to placebo (n=2494), 10% of valsartan patients discontinued for adverse events vs. 7% of placebo patients.

The table shows adverse events in double blind short term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3282)	Placebo (n=2740)
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Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Other adverse events with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: There are rare reports of angioedema;

Digestive: Elevated liver enzymes and very rare reports of hepatitis;

Renal: Impaired renal function;

Clinical Laboratory Tests: Hyperkalemia;

Dermatologic: Alopecia.

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan treated patients compared to 0.9% of placebo treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver function tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan treated patients compared to 5.1% of placebo treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan treated patients compared to 6.3% of placebo treated patients.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION**Hypertension**

The recommended starting dose of Diovan® (valsartan) is 80 mg once daily when used as monotherapy in patients who are not volume-depleted. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required, the dosage may be increased to 160 mg or 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

Heart Failure

The recommended starting dose of Diovan is 40 mg twice daily. (This dose is available only in tablet form.) 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.

HOW SUPPLIED

Diovan® (valsartan) is available as opaque capsules containing valsartan 80 mg or 160 mg. Both strengths are packaged in bottles of 100 capsules and unit dose blister packages (boxes of 10 strips of 10 capsules). Capsules are imprinted as follows:

Capsule	Color	Imprint	NDC	
			Bottle	Blister
80 mg	Light pink and	CG FZF	0083-4000-01	0083-4000-61
160 mg	Dark grey	CG GOG	0083-4001-01	0083-4001-61

NDA 20-665/S-016

NDA 21-283/S-001

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Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Protect from moisture.

Dispense in tight container (USP).

PI - CHF Proposed capV2.doc

REV: CHF NDA Printed in U.S.A.

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

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Diovan®
valsartan
Tablets
Rx only
Prescribing Information

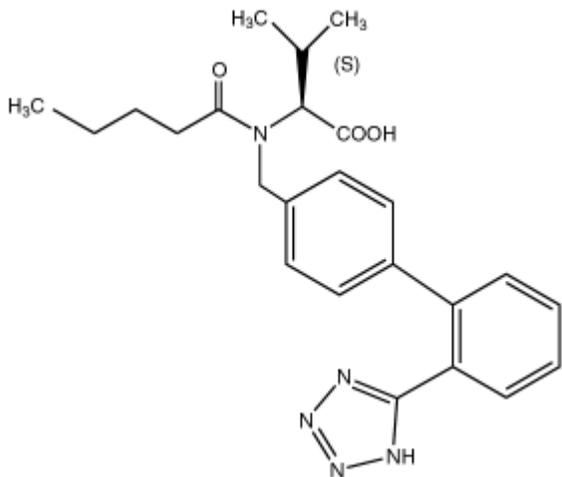
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Diovan® (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine. Its empirical formula is C₂₄H₂₉N₅O₃, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as tablets for oral administration, containing 40 mg, 80 mg, 160 mg or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT₁ receptor than for the AT₂ receptor. The increased plasma levels of angiotensin II following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT₁ receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Diovan is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

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).

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L),

indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations

Pediatric: The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics and Clinical Effects

Hypertension

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Diovan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of

response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF <40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4

mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the table below.

	Placebo N=2499	Valsartan N=2511	Hazard ratio (95% CI)	Nominal p-value
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.80
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE inhibitor		With ACE inhibitor	
	Placebo (N=181)	Valsartan (N=185)	Placebo (N=2318)	Valsartan (N=2326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo N=181	Valsartan N=185	Hazard ratio (95% CI)
Components of HF morbidity			
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)
CHF therapy	1(0.6%)	0 (0.0%)	---
CHF hospitalization	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)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Concomitant use of an ACE inhibitor, a beta-blocker, and valsartan was associated with a worse outcome for heart failure morbidity, as shown in the following table.

	Placebo (N=816)	Valsartan (N=794)	Hazard ratio (95% CI)
Heart failure morbidity	179 (21.9%)	202 (25.4%)	1.18 (0.97, 1.45)

All-cause mortality	97 (11.9%)	129 (16.2%)	1.42 (1.09, 1.85)
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It is not known if this is a reproducible effect or a chance occurrence. The use of a beta-blocker did not appear to influence the effect of valsartan in patients not receiving an ACE inhibitor.

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

INDICATIONS AND USAGE

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 CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure for details.)

CONTRAINDICATIONS

Diovan® (valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan® (valsartan) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of

the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension in valsartan treated patients was 5.5% compared to 1.8% in placebo treated patients.

PRECAUTIONS

General

Impaired Hepatic Function: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan® (valsartan) to these patients.

Impaired Renal Function - Hypertension: In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Impaired Renal Function – Heart Failure: 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. Similar outcomes have been reported with Diovan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). Evaluation of patients with heart failure should always include assessment of renal function.

Concomitant Therapy in Patients with Heart Failure: In patients with heart failure, concomitant use of Diovan, an ACE inhibitor, and a beta blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable heart failure outcome (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure).

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (eg. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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.)

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In the controlled clinical trials of valsartan, 1214 (36.2%) of hypertensive patients treated with valsartan were \geq 65 years and 265 (7.9%) were \geq 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.

ADVERSE REACTIONS

Hypertension

Diovan® (valsartan) has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with

Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole: Allergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipation, dry mouth, dyspepsia, and flatulence

Musculoskeletal: Back pain, muscle cramps, and myalgia

Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Heart Failure

The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2506) to placebo (n=2494), 10% of valsartan patients discontinued for adverse events vs. 7% of placebo patients.

The table shows adverse events in double blind short term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3282)	Placebo (n=2740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Other adverse events with an incidence greater than 1% and greater than placebo included, headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: There are rare reports of angioedema;

Digestive: Elevated liver enzymes and very rare reports of hepatitis;

Renal: Impaired renal function;

Clinical Laboratory Tests: Hyperkalemia;

Dermatologic: Alopecia.

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan treated patients compared to 0.9% of placebo treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver function tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan treated patients compared to 5.1% of placebo treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan treated patients compared to 6.3% of placebo treated patients.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION

Hypertension

The recommended starting dose of Diovan® (valsartan) is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

Heart Failure

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, 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.

HOW SUPPLIED

Diovan® (valsartan) is available as tablets containing valsartan 40 mg, 80 mg, 160 mg or 320 mg. All strengths are packaged in bottles and unit dose blister packages (10 strips of 10 tablets) as described below.

40-mg tablets are round and slightly convex with bevelled edges. 80-, 160-, and 320-mg tablets are almond-shaped with bevelled edges. All tablets are unscored.

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Tablet	Color	Deboss Side 1 2	NDC 0078-xxx-xx		
			Bottle of		Blister
			30	100	
40 mg	Yellow	NVR DO	376-15	-	376-06
80 mg	Pale red	NVR DV	-	358-05	358-06
160 mg	Grey-orange	NVR DX	-	359-05	359-06
320 mg	Dark grey-violet	NVR DXL	-	360-05	360-06

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

[See USP controlled room temperature.]

Protect from moisture.

Dispense in tight container (USP).

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/s/

Robert Temple
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