CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20665/S004

FINAL PRINTED LABELING

NOVARTIS

C98-49 (Rev. 10/98)

Diovan®

valsartan

Capsules

Rx only

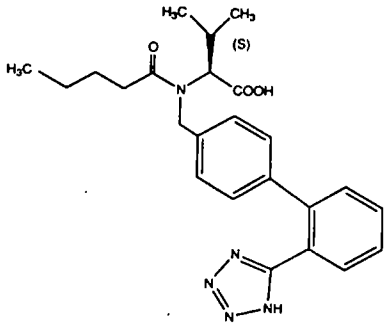
Prescribing Information

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 AT_1 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 $C_{24}H_{29}N_5O_3$, 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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 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.
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

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.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Diovan 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 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 non-stress 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/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hypotension in Volume- and/or Salt-Depleted Patients

Excessive reduction of blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension. 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 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.

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 to these patients.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), 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. Diovan would be expected to behave similarly.

In studies of ACE inhibitors in 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 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.

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.

Diovan®
valsartan

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.

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/m^2 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/m^2 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 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.

ADVERSE REACTIONS
Diovan 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.

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.

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.
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: Greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. No patient treated with valsartan discontinued therapy for hyperkalemia.

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/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION

The recommended starting dose of Diovan 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.

HOW SUPPLIED

Diovan is available as capsules containing valsartan 80 mg or 160 mg. Both strengths are packaged in bottles of 100 capsules and 4000 capsules and unit dose blister packages. Capsules are imprinted as follows:

80 mg Capsule - Light grey/light pink opaque, imprinted CG FZF

Bottles of 100	NDC 0083-4000-01
Bottles of 4000	NDC 0083-4000-41
Unit Dose (blister pack)	NDC 0083-4000-61
Box of 100 (strips of 10)	

160 mg Capsule - Dark grey/light pink opaque, imprinted CG GOG

Bottles of 100	NDC 0083-4001-01
Bottles of 4000	NDC 0083-4001-41
Unit Dose (blister pack)	NDC 0083-4001-61
Box of 100 (strips of 10)	

Store below 30°C (86°F). Protect from moisture.
Dispense in tight container (USP).

Printed in U.S.A. C98-49 (Rev. 10/98)

NOVARTIS

Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

666760

APPROVED

MAR 6 1998

Diovan HCT™

C98-10 (Rev. 2/98)
666760

valsartan and hydrochlorothiazide
Combination Tablets

80 mg/12.5 mg
160 mg/12.5 mg

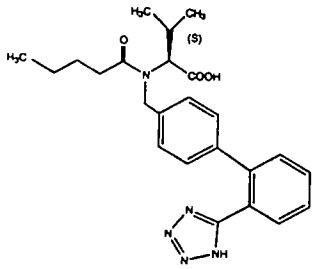
Prescribing Information

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 HCT should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

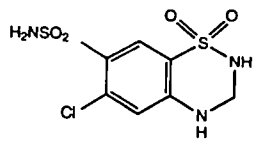
Diovan HCT is a combination of valsartan, an orally active, specific angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Valsartan, a nonpeptide molecule, 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 $C_{24}H_{29}N_5O_3$, 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.

Hydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is $C_7H_8ClN_3O_4S_2$, its molecular weight is 297.73, and its structural formula is



Diovan HCT tablets are formulated for oral administration with a combination of 80 mg or 160 mg of valsartan and 12.5 mg of hydrochlorothiazide USP. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, 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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 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.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics

Valsartan

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

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).

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.

Distribution

Valsartan

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.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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.

Race: Pharmacokinetic differences due to race have not been studied.

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).

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours.

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

Valsartan - Hydrochlorothiazide

In controlled clinical trials including over 1500 patients, 730 patients were exposed to valsartan (80 and 160 mg) and concomitant hydrochlorothiazide (12.5 and 25 mg). A factorial trial compared the combinations of 80/12.5 mg, 80/25 mg, 160/12.5 mg and 160/25 mg with their respective components and placebo. The combination of valsartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 15-21/8-11 mmHg at 80/12.5 mg to 160/25 mg, compared to 7-10/4-6 mmHg for valsartan 80 mg to 160 mg and 6-10/3-5 mmHg for hydrochlorothiazide 12.5 mg to 25 mg, alone.

In another controlled trial the addition of hydrochlorothiazide 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 mg and 25 mg of hydrochlorothiazide, respectively, compared to valsartan 80 mg alone.

The maximal antihypertensive effect was attained 4 weeks after the initiation of therapy, the first time point at which blood pressure was measured in these trials.

In long-term follow-up studies (without placebo control) the effect of the combination of valsartan and hydrochlorothiazide appeared to be maintained for up to two years. The antihypertensive effect is independent of age or gender. The overall response to the combination was similar for black and non-black patients.

There was essentially no change in heart rate in patients treated with the combination of valsartan and hydrochlorothiazide in controlled trials.

Valsartan

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 valsartan 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 nigher 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 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.

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.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

INDICATIONS AND USAGE

Diovan HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Diovan HCT is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

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 HCT 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 Diovan HCT as soon 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 intraamniotic environment.

If oligohydramnios is observed, Diovan HCT 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.

Valsartan - Hydrochlorothiazide in Animals

There was no evidence of teratogenicity in mice, rats, or rabbits treated orally with valsartan at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 188, 31 and 3 mg/kg/day. These non-teratogenic doses in mice, rats and rabbits, respectively, represent 18, 7 and 1 times the maximum recommended human dose (MRHD) of valsartan and 38, 13 and 2 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 160 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

Fetotoxicity was observed in association with maternal toxicity in rats and rabbits at valsartan doses of ≥200 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of ≥63 and 3 mg/kg/day. Fetotoxicity in rats was considered to be related to decreased fetal weights and included fetal variations of sternebrae, vertebrae, ribs and/or renal papillae. Fetotoxicity in rabbits included increased numbers of late resorptions with resultant increases in total resorptions, postimplantation losses and decreased number of live fetuses. The no observed adverse effect doses in mice, rats and rabbits for valsartan were 600, 100 and 3 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of 188, 31 and 1 mg/kg/day. These no adverse effect doses in mice, rats and rabbits, respectively, represent 5, 1.5 and 0.06 times the MRHD of valsartan and 38, 13 and 0.5 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 160 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

Valsartan in Animals

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 18, 12 and 0.2 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 160 mg/day and a 60-kg patient.)

Hydrochlorothiazide in Animals

Under the auspices of the National Toxicology Program, pregnant mice and rats that received hydrochlorothiazide via gavage at doses up to 3000 and 1000 mg/kg/day, respectively, on gestation days 6 through 15 showed no evidence of teratogenicity. These doses of hydrochlorothiazide in mice and rats represent 608 and 405 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume- and/or Salt-Depleted Patients

Excessive reduction of blood pressure was rarely seen (0.5%) in patients with uncomplicated hypertension treated with Diovan HCT. 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 HCT, or the treatment should start under close medical supervision.

If 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.

Hydrochlorothiazide

Impaired Hepatic Function

Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, Lithium).

PRECAUTIONS

Serum Electrolytes

Valsartan - Hydrochlorothiazide

In the controlled trials of various doses of the combination of valsartan and hydrochlorothiazide the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 4.5%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.3%. Two patients (0.3%) discontinued from a trial for decreases in serum potassium.

In controlled clinical trials of Diovan HCT, the average change in serum potassium was near zero in subjects who received Diovan HCT 160/12.5 mg, but the average subject who received Diovan HCT 80/12.5 mg, 80/25 mg or 160/25 mg experienced a mild reduction in serum potassium.

In clinical trials, the opposite effects of valsartan (80 or 160 mg) and hydrochlorothiazide

(12.5 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Hydrochlorothiazide

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function

Valsartan

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 valsartan to these patients.

Impaired Renal Function

Valsartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), 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. Valsartan would be expected to behave similarly.

In studies of ACE inhibitors in 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 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 valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

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.

Symptomatic Hypotension: A patient receiving Diovan HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Diovan HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving Diovan HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Drug Interactions

Valsartan

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.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics - Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin) - Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs - Additive effect or potentiation.

Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.

Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) - Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant.

Lithium - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Diovan HCT.

Non-steroidal anti-inflammatory Drugs - In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Diovan HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Valsartan - Hydrochlorothiazide

No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of valsartan and hydrochlorothiazide. However, these studies have been conducted for valsartan as well as hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any adverse interaction between valsartan and hydrochlorothiazide.

Valsartan

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 5 and 12 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 160 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 about 12 times the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 160 mg/day and a 60-kg patient.)

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella Typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcgm/mL, and in the Aspergillus Nidulans non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

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. Thiazides appear in human milk. 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 Diovan HCT, 117 (16%) of patients treated with valsartan-hydrochlorothiazide were ≥65 years and 16 (2.2%) were ≥75 years. No overall difference in the efficacy or safety of valsartan-hydrochlorothiazide was observed between these patients

and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Diovan HCT has been evaluated for safety in more than 1,300 patients, including over 360 treated for over 6 months, and 170 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 HCT was comparable to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 3.6% of valsartan-hydrochlorothiazide patients and 4.3% of placebo patients. The most common reasons for discontinuation of therapy with Diovan HCT were headache, fatigue and dizziness.

The adverse experiences that occurred in controlled clinical trials in at least 2% of patients treated with Diovan HCT and at a higher incidence in valsartan-hydrochlorothiazide (n=730) than placebo (n=93) patients included dizziness (9% vs 7%), viral infection (3% vs 1%), fatigue (5% vs 1%), pharyngitis (3% vs 1%), coughing (3% vs 0%) and diarrhea (3% vs 0%).

Headache, upper respiratory infection, sinusitis, back pain and chest pain occurred at a more than 2% rate but at about the same incidence in placebo and valsartan-hydrochlorothiazide patients.

Dose-related orthostatic effects were seen in less than 1% of patients. A dose-related increase in the incidence of dizziness was observed in patients treated with Diovan HCT from 80/12.5 mg (6%) to 160/25 mg (16%).

Other adverse experiences that have been reported with valsartan-hydrochlorothiazide (>0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

Body as a Whole: Allergic reaction, anaphylaxis, asthenia, and dependent edema.
Cardiovascular: Palpitations, syncope, and tachycardia.
Dermatologic: Flushing, rash, sunburn, and increased sweating.
Digestive: Increased appetite, constipation, dyspepsia, flatulence, dry mouth, nausea, abdominal pain, and vomiting.
Metabolic: Dehydration and gout.
Musculoskeletal: Arthralgia, muscle cramps, muscle weakness, arm pain, and leg pain.
Neurologic and Psychiatric: Anxiety, depression, insomnia, decreased libido, paresthesia, and somnolence.
Respiratory: Bronchospasm, dyspnea, and epistaxis.
Special Senses: Tinnitus, vertigo, and abnormal vision.
Urogenital: Dysuria, impotence, micturition frequency, and urinary tract infection.

Valsartan

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, hydrochlorothiazide, or lisinopril were 20%, 19%, 69% respectively ($p < 0.001$).

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

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body As A Whole: weakness;
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;
Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing anglitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions;
Metabolic: hyperglycemia, glycosuria, hyperuricemia;
Musculoskeletal: muscle spasm;
Nervous System/Psychiatric: restlessness;
Renal: renal failure, renal dysfunction, interstitial nephritis;
Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;
Special Senses: transient blurred vision, xanthopsia.

Clinical Laboratory Test Findings

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

Creatinine: Minor elevations in creatinine occurred in 1.4% of patients taking Diovan HCT and 1.1% given placebo in controlled clinical trials.
Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.1% and 1.0%, respectively, of Diovan HCT patients, compared with 0.0% in placebo-treated patients.
Liver function tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT-treated patients.
Neutropenia: Neutropenia was observed in 0.6% of patients treated with Diovan HCT and 0.0% of patients treated with placebo.
Serum Electrolytes: See PRECAUTIONS.

OVERDOSAGE

Valsartan - Hydrochlorothiazide

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 dialysis.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 93 and 56 times the maximum recommended human dose (MRHD) of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 160 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

Valsartan

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 (31 and 18 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 160 mg/day and a 60-kg patient.)

Hydrochlorothiazide

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, which represents 2027 and 4054 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION

The recommended starting dose of valsartan is 80 mg once daily when used as monotherapy in patients who are not volume depleted. Valsartan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day. Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily, and can be given at doses of 12.5 mg to 25 mg as Diovan HCT.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of valsartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of valsartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Replacement Therapy: The combination may be substituted for the titrated components.

Dose titration by Clinical Effect: Diovan HCT is available as tablets containing either valsartan 80 mg or 160 mg and hydrochlorothiazide 12.5 mg. A patient whose blood pressure is not adequately controlled with valsartan monotherapy (see above) may be switched to Diovan HCT, valsartan 80 mg/hydrochlorothiazide 12.5 mg once daily. If blood pressure remains uncontrolled after about 3-4 weeks of therapy, either valsartan or both components may be increased depending on clinical response. There are no studies evaluating doses of valsartan greater than 160 mg in combination with hydrochlorothiazide 25 mg.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to Diovan HCT (valsartan 80 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to Diovan HCT should be subsequently evaluated and if blood pressure remains uncontrolled after 3-4 weeks of therapy, the dose may be titrated up to valsartan 160 mg/hydrochlorothiazide 25 mg.

The maximal antihypertensive effect is attained about 4 weeks after initiation of therapy.

Patients with Renal Impairment: The usual regimens of therapy with Diovan HCT may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Diovan HCT is not recommended.

Patients with Hepatic Impairment: Care should be exercised with dosing of Diovan HCT in patients with hepatic impairment.

Other: No initial dosage adjustment is required for elderly patients.

Diovan HCT may be administered with other antihypertensive agents.

Diovan HCT may be administered with or without food.

HOW SUPPLIED

Diovan HCT is available as tablets containing either valsartan 80 mg or 160 mg and hydrochlorothiazide 12.5 mg. Both strengths are packaged in bottles of 100 tablets and 4000 tablets and unit dose blister packages. Tablets are imprinted as follows:

80/12.5 mg Tablet - Light orange, imprinted CG on one side HGH on the other

Bottles of 100	NDC 0078-0314-05
Bottles of 4000	NDC 0078-0314-97
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0078-0314-06

160/12.5 mg Tablet - Dark red, imprinted CG on one side HHH on the other

Bottles of 100	NDC 0078-0315-05
Bottles of 4000	NDC 0078-0315-97
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0078-0315-06

Storage: Store below 30°C (86°F). Protect from moisture.
Dispense in tight container (USP).

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