

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-665 /SE1-016	SUBMISSION DATES	4/27/01 5/29/01 7/23/01
	21-283 /SE1- 001		
CATEGORY:	4P		
TYPE:	Efficacy supplement for heart failure		
BRAND NAME:	Diovan®		
GENERIC NAME:	valsartan		
ALTERNATE NAMES :	GCP 48933		
DOSAGE STRENGTH:	40, 80, 160, 320 mg capsules and 40 mg tablet		
SPONSOR:	Novartis		
DPE:	I		
PRIMARY REVIEWERS:	B. Nhi Nguyen, Pharm.D. Shari Targum, M.D.		
DPE TEAM LEADER:	Patrick Marroum, Ph.D.		

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RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-665, and NDA 21-283 and finds the clinical pharmacology and biopharmaceutics section acceptable.

We recommend a bioequivalence waiver be granted for the 40 mg tablet. The 40 mg tablet should have similar dissolution specifications as the other strengths:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C

Apparatus: USP II (paddle)

Speed: 50 rpm

Specifications: $Q = [\quad]$ in 30 minutes

OCPB briefing held on August 28, 2001.

(Mehul Mehta, Patrick Marroum, and Nhi Nguyen were present.)

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FT Initialed by Patrick Marroum, Ph.D. _____

CC list: HFD-110: NDA 20-665 (SE1-016) and NDA 21-283 (SE1-001); HFD-860: (Mehta);
CDER Central Document Room

SUMMARY

Novartis submitted a heart failure efficacy supplement (SE1-016) to NDA 20-665, valsartan capsules (Diovan®), an angiotensin II receptor antagonist of the AT_I receptor subtype. The efficacy supplement for NDA 20-665 contains five controlled studies (protocol 104, 106, 107, 107a, 103 and 110) and two descriptive pharmacokinetic studies, a single dose (protocol 102) and a multiple dose (protocol 105) study in heart failure patients.

Valsartan is approved for the treatment of hypertension and is currently available in 80 and 160 mg hard gelatin capsules. After approval of the CHF efficacy supplement, the sponsor intends to remove the capsules, and market film-coated tablets. The sponsor recently received approval for the 80, 160 and 320 mg tablets for the treatment of hypertension under NDA 21-283. The sponsor demonstrated bioequivalence of 2x 160 mg capsules with the 320 mg tablets and received biowaivers for the 80 and 160 mg tablets. Since the proposed starting dose for CHF is 40 mg q 12 hours, the sponsor is seeking a BE waiver for the 40 mg tablet (NDA 21-283 /SE1-001).

The pharmacokinetics are similar between patients with CHF and healthy volunteers with respect to linearity, T_{max} (~3 hours), T_{1/2} (~6.5 hours) and age effects. Linearity is evident with twice daily doses and single doses of 40 – 160 mg. Valsartan clearance was ~ 10-20% lower in elderly patients with CHF compared to young patients with CHF.

There are several differences in valsartan pharmacokinetics between healthy volunteers and patients with CHF. Clearance of valsartan appears to be reduced ~50% in patients with CHF compared to healthy subjects (~4.5 L/hr vs. 2.2 L/hr, respectively). C_{max} and AUC are ~1.3 – 2 x higher in patients with CHF compared to healthy volunteers. Accumulation of valsartan is slightly greater (1.7 vs. 1.3) in patients with CHF when dosed at 40 to 160 mg twice daily compared to once daily in hypertensives.

A biowaiver for the 40 mg tablet is granted since the tablets are compositionally proportional, valsartan exhibits linear pharmacokinetic characteristics, and the in vitro dissolution profiles are similar across the different strengths. The approved specifications for all dosage strengths are:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C

Apparatus: USP II (paddle)

Speed: 50 rpm

Specifications: Q = [] in 30 minutes

Valsartan concentrations were determined by a validated HPLC method. The assay used was precise, accurate, sensitive and linear over the concentration range of 5.0 – 5,000 ng/mL.

APPENDIX I: Review of individual studies

Study 102. An Open-Label, Placebo-Controlled, Dose Ranging Trial to Determine the Acute Central Hemodynamic Effects of CGP 48933 in Patients with Stable, Chronic, Congestive Heart Failure (Phase II) (Protocol date: September 30, 1992)

This study was jointly reviewed with the medical officer, Dr. Shari Targum.

Source: NDA Volume 12 (Study Report and Tables), 13 (Protocol); no .xpt datasets were submitted.

Valsartan and CGP48933 will be used interchangeably in this review.

Primary Objectives:

1. Evaluate, by right heart catheterization, central hemodynamic effects of single, open-label doses of CGP 48933 (valsartan) 10, 20, 40, 80 and 160 mg compared to placebo up to 24 hours after dosing, in patients with stable chronic congestive heart failure with a NYHA classification of III or IV.
2. Evaluate safety and tolerability of single open-label doses of CGP 48933 10, 20, 40, 80, and 160 mg in patients with stable chronic congestive heart failure.

Secondary Objectives:

1. Obtain preliminary information on correlation between plasma levels of CGP 48933 and its acute central hemodynamic effects compared to placebo.
2. Obtain preliminary information on effects of CGP 48933 on plasma renin activity, plasma aldosterone, and plasma angiotensin II concentration up to 24 hours after dosing, compared to placebo, and correlate these effects with its acute hemodynamic actions.

Sites: 3 centers in the US.

Duration: March 12, 1993 (first patient, first visit) to April 4, 1994 (last patient, last visit)

Study Design:

This was a single-dose, open-label, randomized parallel-group study in patients with Class III or IV CHF. Chronic CHF medications were allowed until 2 days prior to dosing; at that time, ACE inhibitors, vasodilators and inotropic agents (except digoxin) were discontinued. On the day of dosing, diuretics were held and digoxin was allowed; antiarrhythmics were allowed throughout the study. Patients were to fast 9 hours prior to dosing. Randomized patients underwent right heart catheterization, via Swan-Ganz catheter, as well as arterial cannulation. After stable baseline hemodynamic measurements, patients were given a single dose of drug or placebo, and central hemodynamic and neurohormonal measurements were taken at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. After all measurements were taken, the lines were removed, patients resumed their prior medications, and were discharged to follow-up one week after dosing.

Figure 1. Treatment algorithm

		CGP 48933 10 mg (N=5)				
		CGP 48933 20 mg (N=4)				
		CGP 48933 40 mg (N=3)				
		CGP 48933 80 mg (N=4)				
		CGP 48933 160 mg (N=5)				
		Placebo (N=4) ↓				
Visit	1	2	3		4	
Day	-14 to -3	-1	0	1	7	
Hour			0	24		

N=number randomized

Inclusion Criteria ¹	Exclusion Criteria
<ul style="list-style-type: none"> • Male or female patients 18 to 80 years. • Chronic stable CHF, present for at least 4 weeks, NYHA Class III or IV, and ejection fraction $\leq 35\%$, determined by MUGA (determined up to 6 weeks prior to enrollment if interval-free of intercurrent events). Patients on background therapy should be on stable doses for at least 2 weeks prior to entry into the trial. • Must be able to tolerate discontinuation of ACE inhibitors, vasodilators, and positive inotropes (except digoxin) for 3 days and diuretics for 24 hours. 	<ul style="list-style-type: none"> • Female patients of childbearing potential. • History of acute MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 4 weeks prior to entry into study. • Angina pectoris requiring more than 5 tablets/week of prn sublingual nitroglycerin. • Clinically significant primary valvular dysfunction. • Presence or history of restrictive cardiomyopathy, constrictive pericarditis, dyspnea of non-cardiac origin, gastrointestinal disease or surgery which would impair drug absorption, any condition/lab abnormality which would interfere with this study. • Complex or life-threatening ventricular arrhythmias. • Clinically significant renal, hepatic, or hematologic disorders, unless consistent with CHF. • Uncontrolled hypertension (BP $\geq 160/100$). • Unstable insulin-dependent diabetes mellitus. • Presence/recent serious psychiatric disorder, personality problem or living condition suggesting that the patient would be unable to participate fully in this trial. • Inability to discontinue long-acting nitrates, positive inotropes, vasodilators, beta blockers, calcium channel blockers, ACE inhibitors and diuretics.

Randomization criteria (patients must meet all criteria in order to be randomized):

1. All baseline hemodynamic measurements were to be repeated at 20 minute intervals until 2 consecutive sets of heart rate (HR), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) measurements were within 10%, respectively. A maximum of 5 sets of measurements were to be done. If the fifth set of measurements was not within 10% of the fourth set, then the patient was to be discontinued from the trial.
2. The patient was to be clinically stable (i.e., no complications from Swan-Ganz or arterial cannula insertion, or change in any concomitant condition).
3. PCWP on the second set of measurements had to be ≥ 15 mm Hg.

¹ Taken from Protocol. Please see Amendments to the Protocol for changes in Inclusion/Exclusion criteria.

Sample Size: This study was to have a total of 36 evaluable patients, defined as those who satisfied entry criteria and completed all visits. There was no sample size calculation.

Primary Efficacy Variable :

Change from baseline in PCWP and CO measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

CO was determined by taking 5 measurements, excluding highest and lowest values, and averaging the remaining 3 values.

Secondary Efficacy Variables:

1. Change from baseline in right atrial pressure (RAP), diastolic, systolic and mean pulmonary artery pressure (PAP), CI, SVR, PVR, SVI, heart rate, and systolic, diastolic and mean systemic blood pressure (MAP) measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
2. Change from baseline, compared to placebo, in plasma renin activity, plasma aldosterone and plasma angiotensin II activity measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
3. CGP 48933 blood levels at 1, 2, 3, 4, 6, 8, and 12 hours after dosing.

CI, SVR, SVI, and PVR were calculated from formulas that were prespecified in the protocol.

Statistical Plan: There were no prespecified statistical analyses or interim analysis.

Safety Variables:

Physical examination (all visits), body weight (all visits), adverse experiences, laboratory testing (CBC, chemistry, urinalysis at Visits 1, 2, 3, 4), 12-lead ECGs (Visits 1 and 3), CXR(Visit 1), MUGA scan (within 6 weeks of Visit 1 or before Visit 2).

Laboratory: Central laboratory (National Health Laboratory).

Amendments to the Protocol (not signed):

1. (not dated) Under “presence of clinically significant renal, hepatic, or hematologic disorders” Specified exclusion criteria of hemoglobin < 10 g/dl.
2. (not dated). Changed entry criteria to “patients who are clinically stable for one week prior to entry into the trial” with stable background medications for 1 week prior to discontinuation of ACE inhibitors and diuretics.

Drug Supply: Drug Supply was provided by Ciba-Geigy. Batch and formulation numbers are as follows:

Table 1. Supply batch and formulation numbers

Treatment group	Batch Number	Formulation Number
Valsartan 10 mg	E-14937	H-3573
Valsartan 20 mg	E-14938	H-3574
Valsartan 40 mg	E-14939	H-3575
Valsartan 80 mg	E-14940	H-3576
Valsartan 160 mg	E-14941	H-3577
Placebo	E-14942	H-3577

Source: Sponsor: Volume 12 (Study report)

Medication was started on Visit 3 (Day 0) after all baseline measurements. All doses were administered in the fasting state with direct supervision.

Assay:

The assay used was precise, accurate, sensitive and linear over the concentrations of 5 – 3000 ng/mL (see table below). Plasma valsartan concentrations were determined by a validated HPLC method. The analysis was done at the laboratories of Bioanalytics and Pharmacokinetics, Rueil-Malmaison, France from January 24, 1994 to March 18, 1994.

Table 2. Quality of assay

	Precision (%)	Accuracy (%)	Sensitivity (ng/mL)	Linearity (ng/mL)
Valsartan	CV < 18%	Within 5%	5.00 – 3000	0.9987

Results:

Patient Disposition:

Thirty two patients were enrolled at Visit 1; seven patients were discontinued prior to randomization (6 did not meet protocol criteria and 1 withdrew consent). Twenty-five patients were randomized at Visit 2 and all completed the study; all were included in efficacy and safety analyses.

Of the baseline characteristics, all were NYHA Class III.

Protocol violations:

A total of 6 randomized patients were noted to have protocol violations related to entry criteria. These included: consecutive PCWP not within 10% (Valsartan 40:1 patient); HR measurements not within 10% (Valsartan 80: 1 patient; Valsartan 160: 1 patient); inducible VT (Valsartan 10: 1 patient); screening visit ejection fraction of 36% (Valsartan 160 mg: 1 patient); woman of childbearing potential (valsartan 40: 1 patient).

Baseline characteristics:

As seen in the table below, this was a mostly male population with a small sample size per treatment arm. Of note, mean baseline PCWP were not uniform, with a higher baseline in the placebo group; hence, interpretations of changes from baseline will be confounded by these baseline differences in the treatment groups.

There are also baseline differences between treatment groups in mean weight, duration of CHF, plasma renin activity as well as plasma aldosterone.

Table 3 . Baseline characteristics

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Male (%)	4 (100)	3 (60)	4 (100)	2 (67)	4 (100)	5 (100)
Race:						
Caucasian	2(50)	2 (40)	1 (25)	0	0	1 (20)
Black	2 (50)	3 (60)	3 (75)	3 (100)	4 (100)	4(80)
Mean age (\pm SD)	48 (10)	44 (12)	54 (9)	50 (10)	55 (15)	54 (13)
Mean weight (lbs)	202 (32)	170 (26)	200 (53)	167 (51)	216 (53)	152 (17)
Mean duration CHF (yrs)	4 (3)	5 (4)	7 (2)	4 (2)	3 (2)	4 (4)
Etiology: Ischemic	1 (25)	1 (20)	1 (25)	0	2 (50)	2 (40)
Idiopathic	1 (25)	2 (40)	1 (25)	2 (67)	2 (50)	1 (20)
Hypertensive	1 (25)	0	2 (50)	0	0	2 (40)
Other	1 (25)	2 (40)	0	1 (33)	0	0

Table 3. Baseline characteristics (cont.)

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Mean Baseline* PCWP (mm Hg) (+ SD)	31.8 (5)	21.0 (8)	26.8 (7)	25 .0(7)	26.5 (6)	24.6 (8)
Mean Baseline* CO (l/min) (+ SD)	3.9(1)	4.2 (1)	3.6(0.6)	4.1 (0.5)	4.0 (1)	4 (0.9)
Mean Baseline* plasma renin activity	6.1(6)	3.1 (4)	2.6 (3)	0.2 (0.2)	3.8 (3)	3 (6)
Mean baseline* plasma Aldosterone	12 (12)	6 (7)	13 (5)	8 (4)	6.8 (4)	17.2 (29)
Mean baseline* plasma Angiotensin II	34.3 (12)	30.6 (20)	31 (22)	27 (8)	48 (31)	34.4 (18)

Source: Volume 12: Tables 7.1:1, 7.1:2 , 8.1:1A, 11.1:2A *Baseline =Pre-Dose value

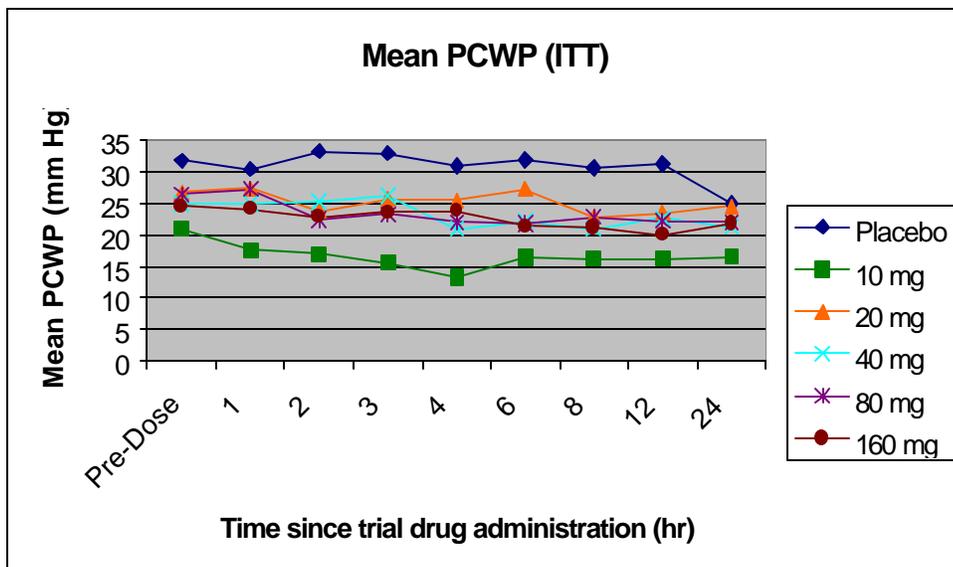
Primary efficacy variable:

Figures 2-5 show the primary efficacy variables, including change from baseline, over time.

The placebo group, with the highest mean value at baseline, also shows the largest decrease at 24 hours.

A dose-response relationship was not seen.

Figure 2. PCWP over time (ITT)



Source for Figures 2 and 3: Volume 12: Tables 8.1:1A, 8.1:1B

Figure 3 . Change from baseline in PCWP

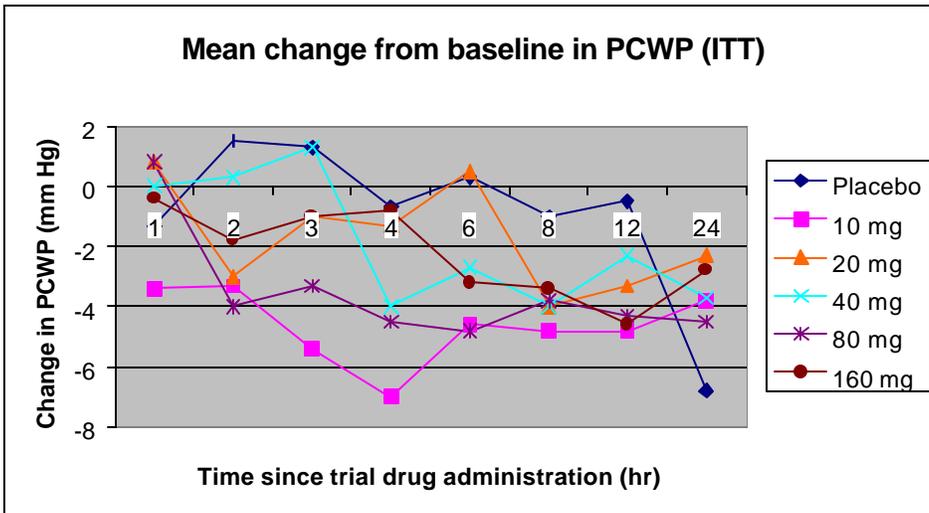
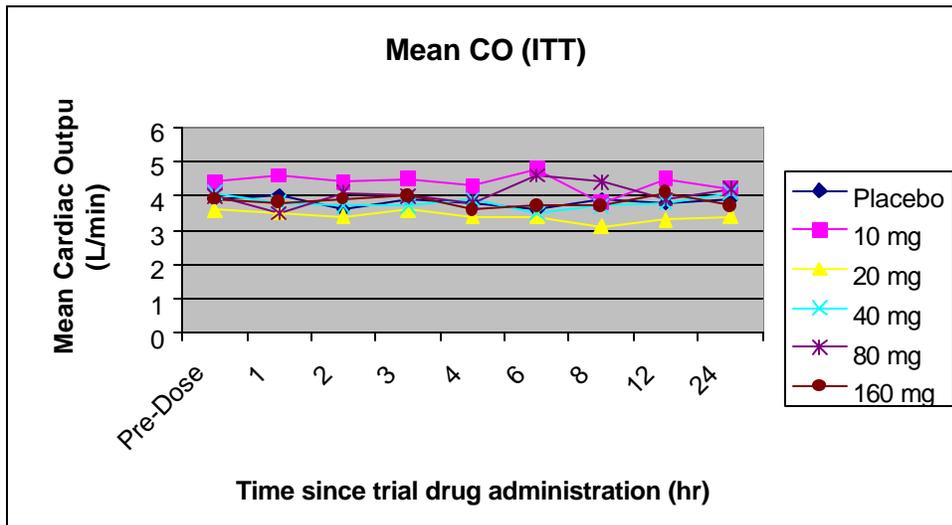


Figure 4 . Cardiac Output (CO) over Time (ITT)



Source for Figures 4 and 5: Volume 12: Tables 8.1:1A and 8.1:1B

Figure 5. Change from baseline in Cardiac Output (ITT)

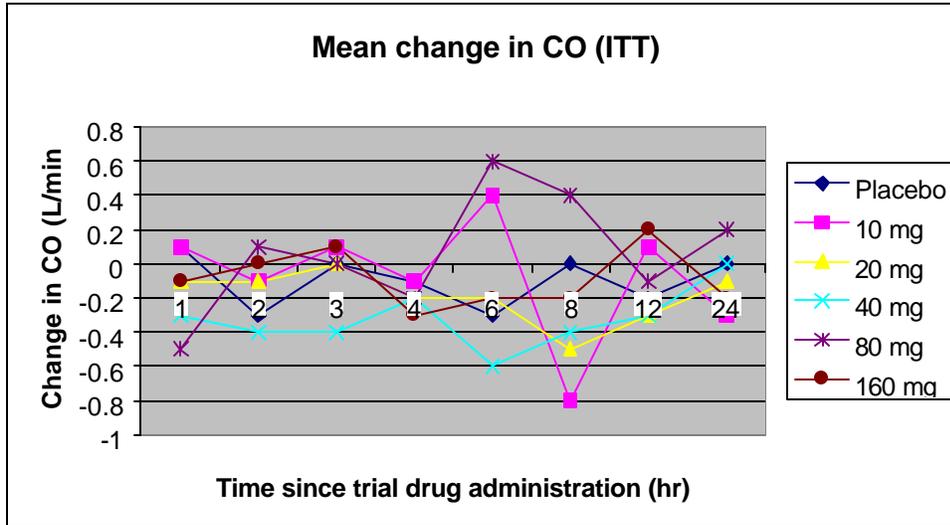


Table 4. Primary Efficacy Variables: Change from Baseline at 24 hours (ITT)

	PCWP	CO
	Change from baseline at 24 hours	Change from baseline at 24 hours
Placebo	-6.8 (2.4)	-0.04 (1.4)
Valsartan 10 mg*	-3.8 (3.3)	-0.3 (0.8)
Valsartan 20 mg	-2.3 (7.4)	-0.1 (0.8)
Valsartan 40 mg	-3.7 (2.1)	-0.03 (0.6)
Valsartan 80 mg	-4.5 (6.9)	0.2 (0.9)
Valsartan 160 mg	-2.8 (7.0)	-0.2 (1.5)

Source: Volume 12: Study Report and Table 8.1:1B * patient 11/507 did not have 24 hour efficacy measurements and was not included in this table.

The above table shows change from baseline at 24 hours for both primary efficacy variables. For PCWP, the placebo group had the highest pre-dose values and showed the largest change from baseline at 24 hours.

Secondary efficacy variables:

The secondary efficacy variables were reviewed. No dose-response relationship or significant changes from baseline compared to placebo could be ascertained; this result may be due in part to the small sample size as well as baseline differences. Therefore, these data will not be presented.

Neurohormone results:

Neurohormone results over time are represented in the next figures. It should be noted that the valsartan 40 mg group, unlike the other groups, shows unusually flat neurohormonal responses. There appear to be elevations in plasma renin activity and angiotensin II at the higher doses, although a clear dose-relationship is not seen.

Figure 6. Plasma Renin Activity (PRA)

Source: Volume 12: Table 11.1:2A

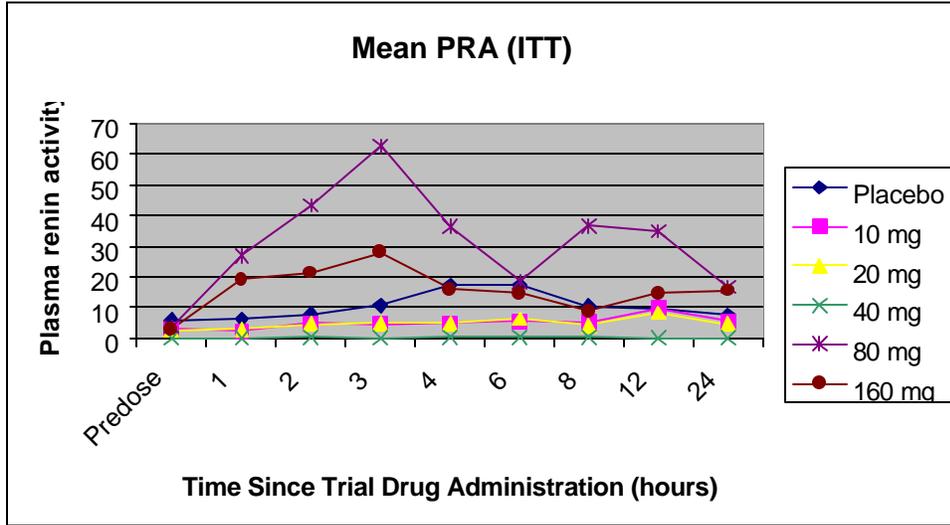
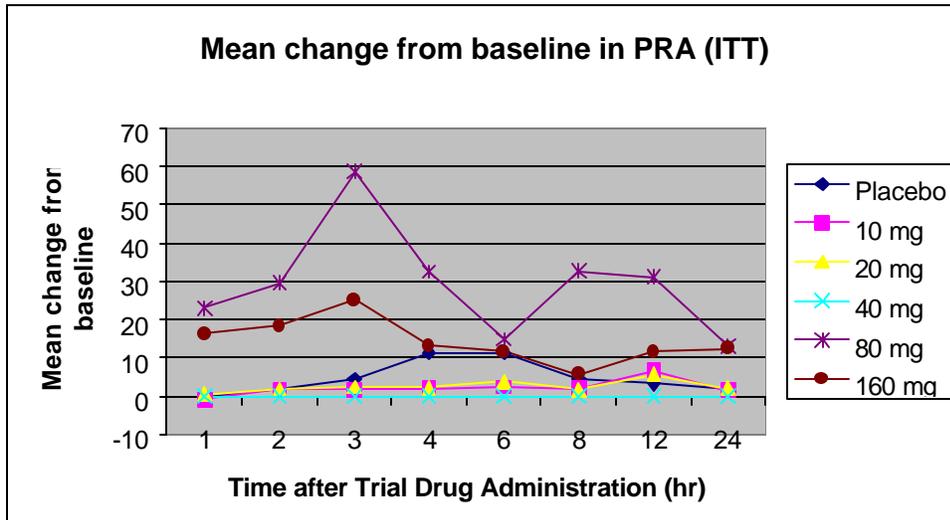


Figure 7. Change from baseline in Plasma Renin Activity (PRA)



Source: Volume 12: Table 11.1:2B

Figure 8. Plasma Angiotensin II

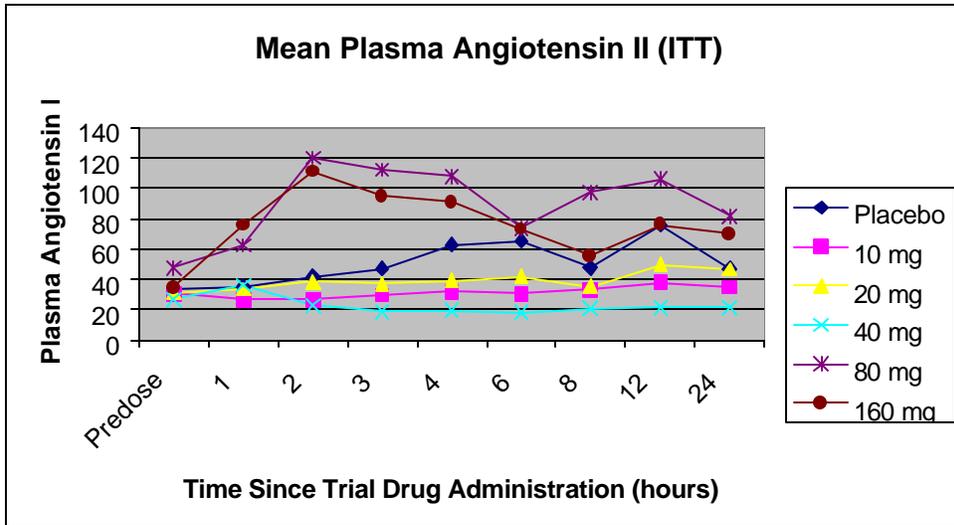
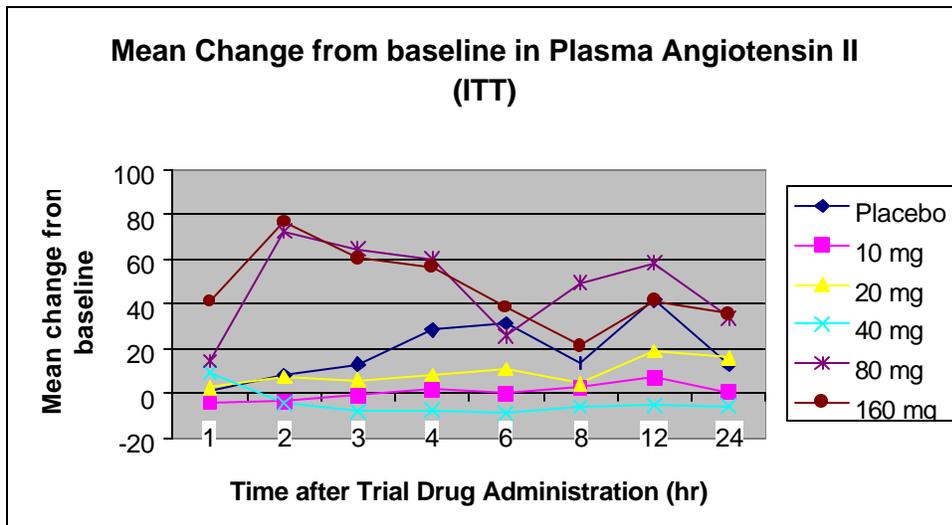


Figure 9. Change from baseline in Angiotensin II



Source: Volume 12: Tables 11.1:2A and B

Figure 10. Plasma Aldosterone

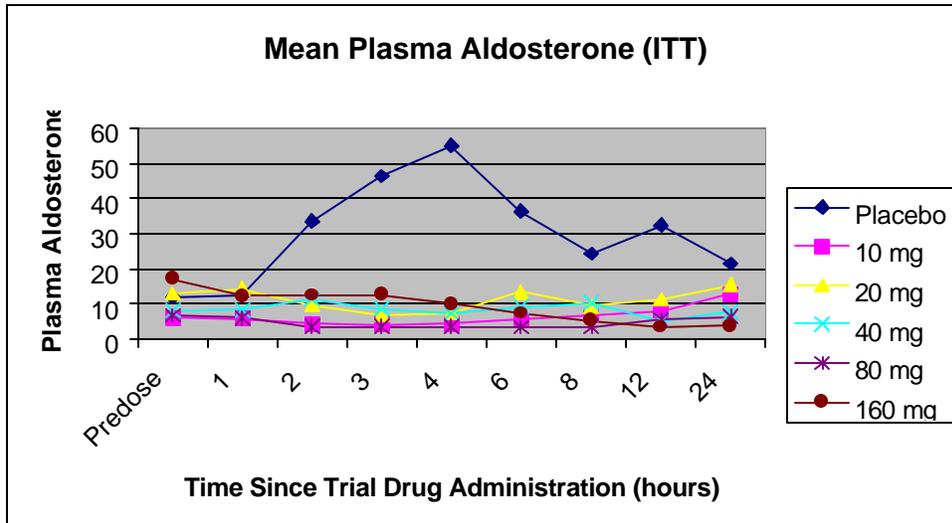
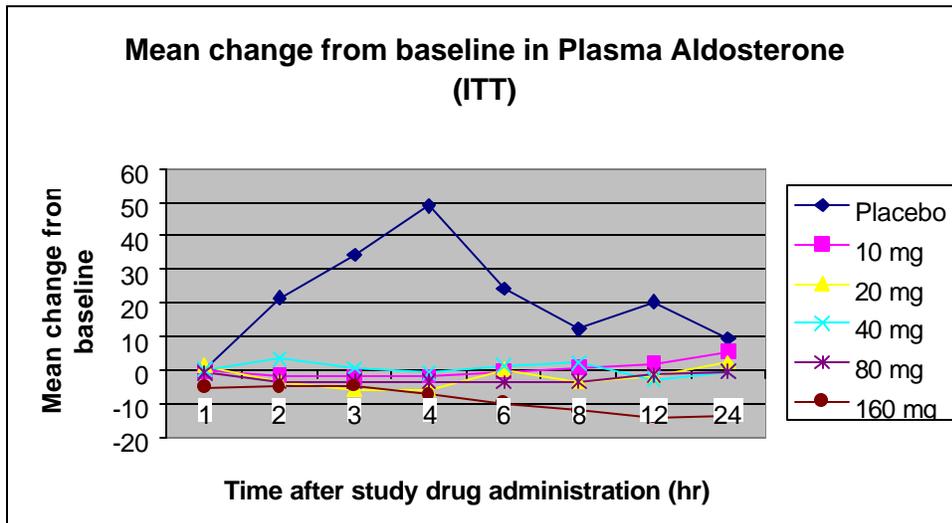


Figure 11. Change from Baseline in Plasma Aldosterone



Pharmacokinetic/pharmacodynamic results

The pharmacokinetic data are highly variable (see table 5). C_{max} was reached ~ 3 hours after dosing.

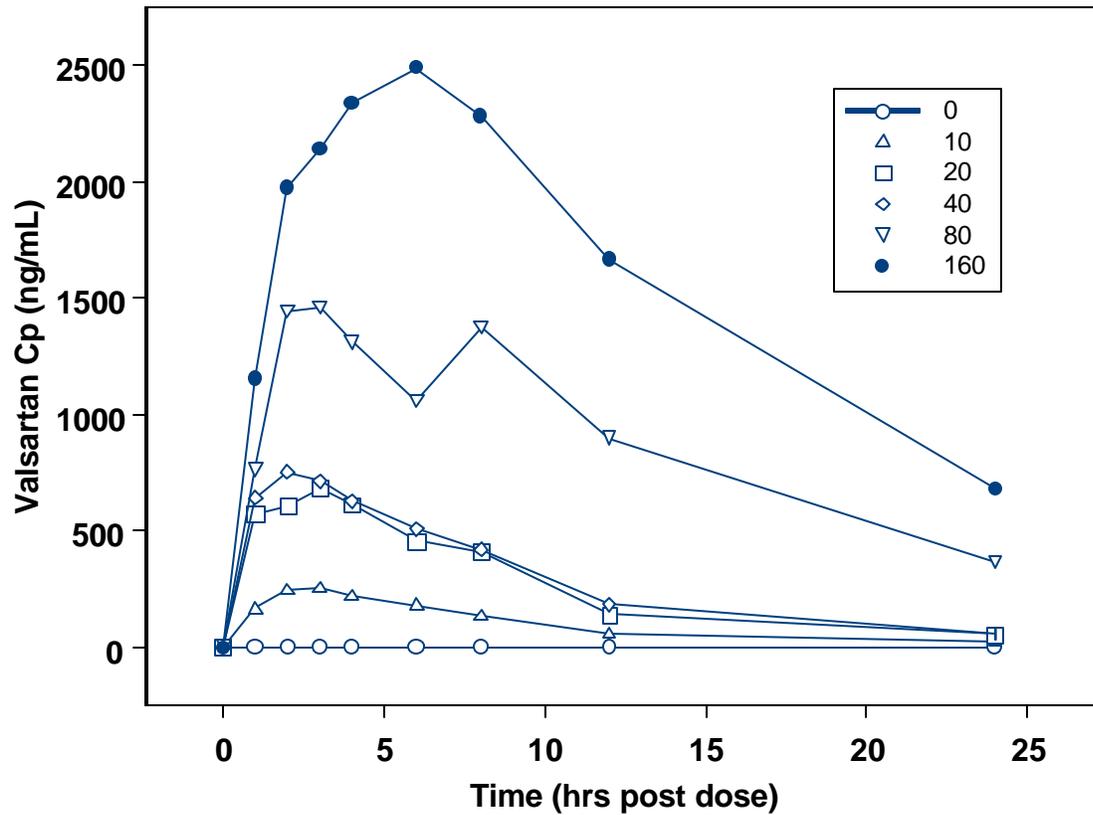
Table 5 . Mean pharmacokinetic parameters

Dose (mg)	N	Cmax (ng/ml)			Tmax	(hr)	AUC (0-24 hr) ng x hr/ml		
		Mean	SD	CV (%)	Median	Range	Mean	SD	CV (%)
10	5	280	68	24	3	2-6	2380	370	16
20	2	684	149	22	2.5	2-3	6380	2750	43
40	3	843	308	36	2	1-8	7150	1430	20
80	4	2150	1490	69	3	2-8	21200	18900	89
160	4	2770	1130	41	6	1-6	38000	25000	66

Source: Sponsor: Volume 12: Study Report

Valsartan exhibits a 2-compartment pharmacokinetic model as shown by the shape of the plasma concentrations time curves in Figure 12.

Figure 12. Valsartan plasma concentration vs. time after single dose



Individual Cmax and AUC were fitted using NONMEM (ver 5.0, level 1.1) to the following equation:

$$Y = \alpha * \text{Dose}^\beta$$

where Y is the predicted Cmax or AUC, α is the slope of the fit and β determines the linearity of the fit. The parameter estimates are shown in Table 9.

Single doses of valsartan are dose proportional over the range of 10 mg to 160 mg. β for both Cmax and AUC are close to one, suggesting that valsartan exhibits linear pharmacokinetics over the concentration range of 0-2500 ng/mL. The 95% confidence interval for Cmax is (0.732, 1.128) and for AUC is (0.962, 1.258). The residual error estimation is ~43% and ~50% for Cmax and AUC, respectively, implying that a considerable portion of the variability is unexplained by the model. Although valsartan exhibits linear pharmacokinetics, it should be noted that the pharmacokinetics are quite variable.

Table 6 . Summary of model parameter estimates

	Cmax (ng/mL)		AUC (ng*hr/mL)	
	a	b	a	b
Mean	31.9	0.93	165	1.11
SE (%)	26.3 %	9.4	27.6 %	8.4 %
Residual error (CV%)	42.5 %		50.5 %	
SE (%)	28.2 %		30.0 %	

Figure 13 . Observed and predicted AUC at five different doses

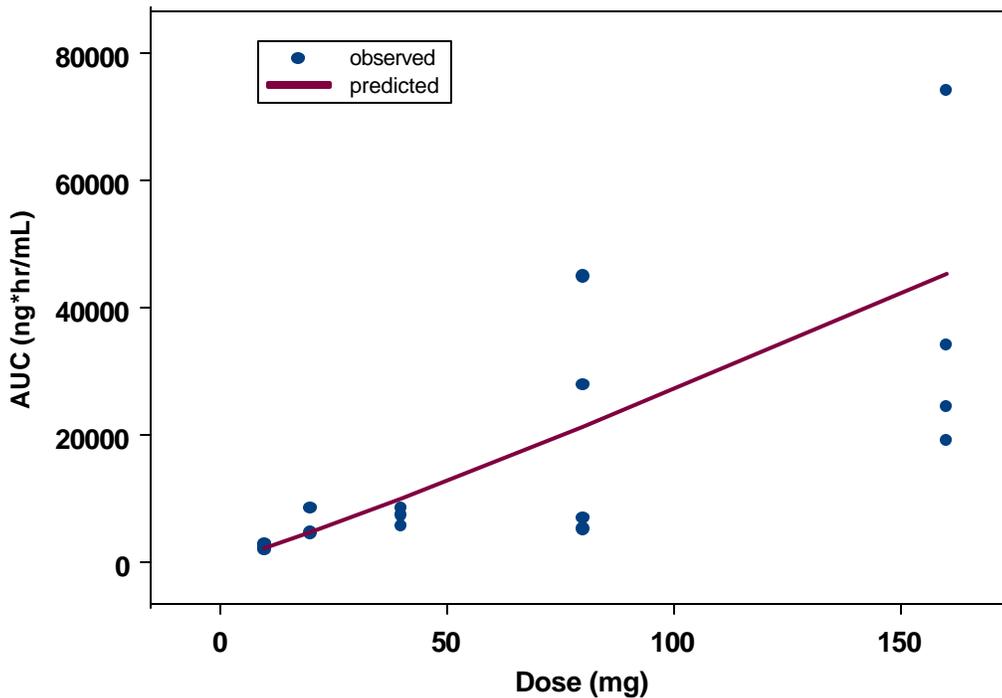
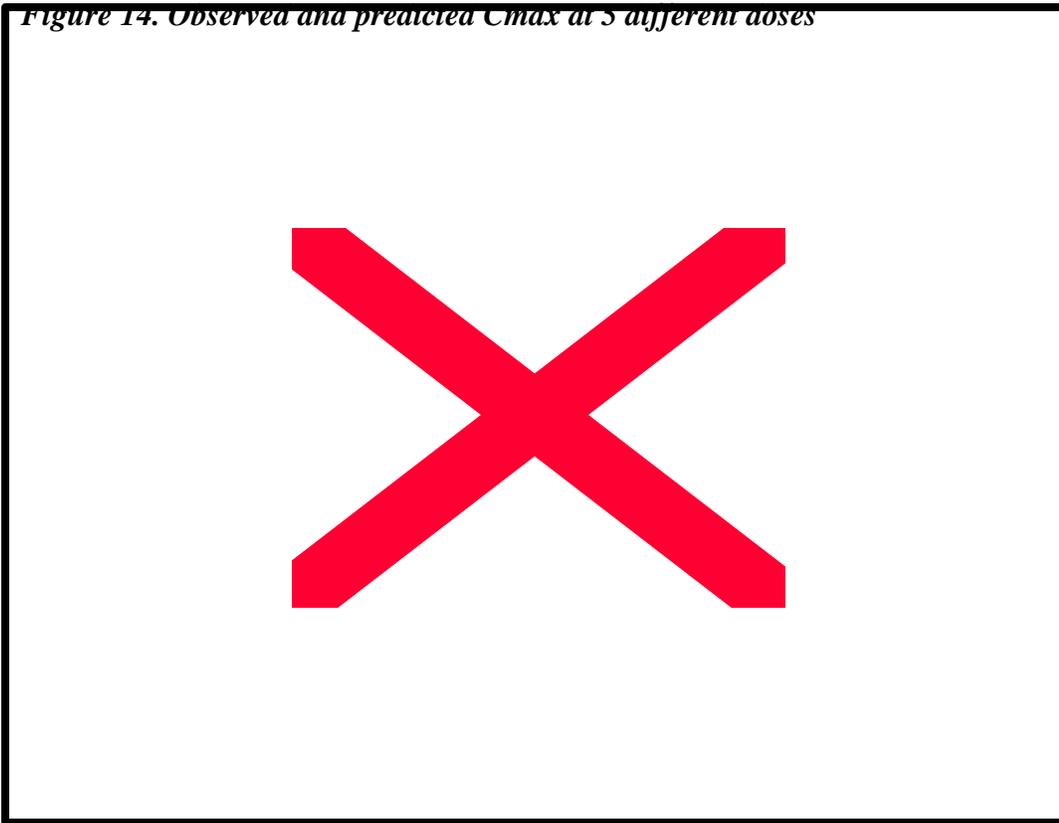


Figure 14. Observed and predicted Cmax at 5 different doses



There was not an evident PK/PD relationship with PCWP or CO.

Figure 15. Mean PCWP and valsartan concentration relationship

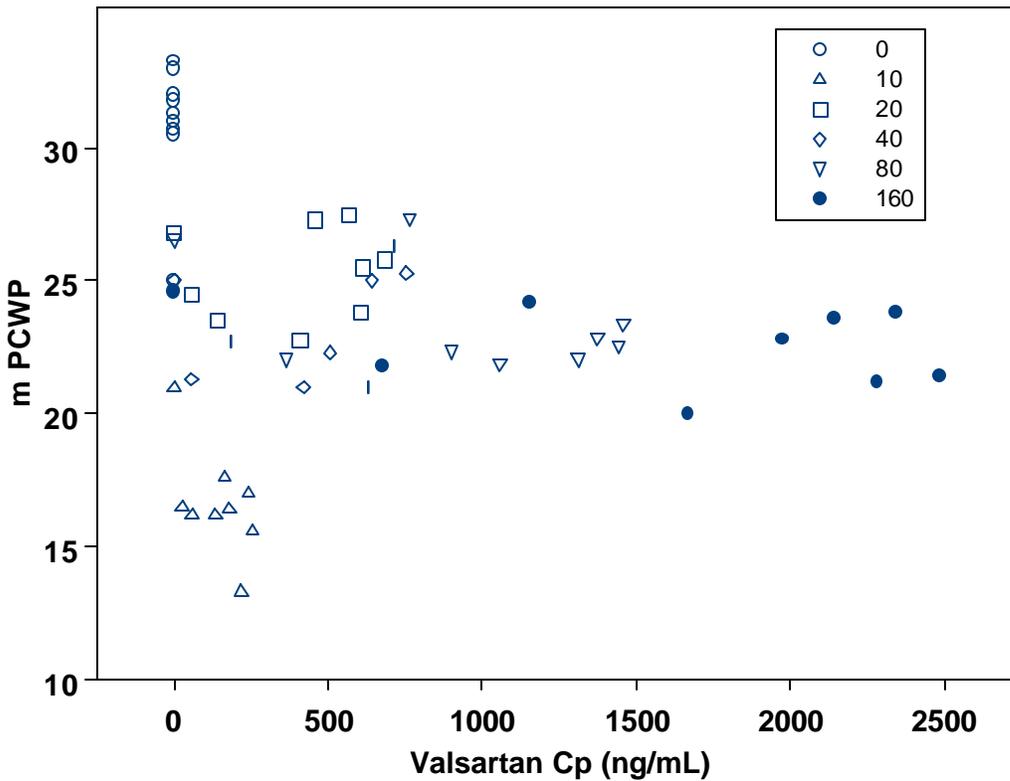
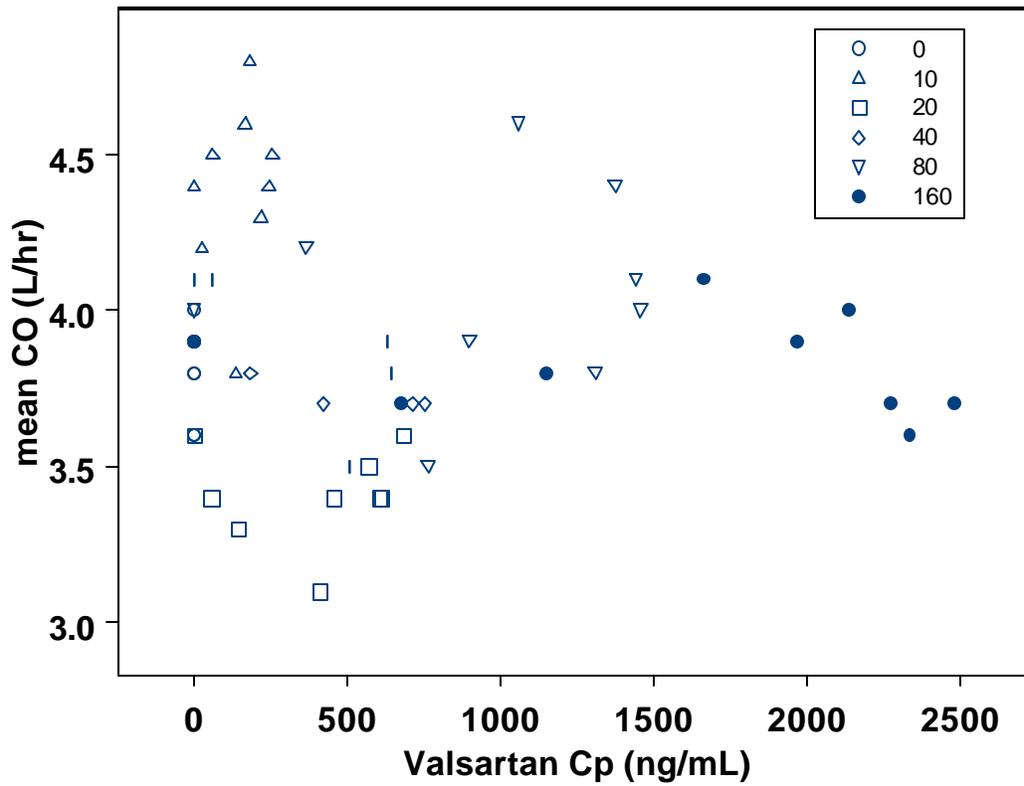


Figure 16. Mean CO and valsartan concentration relationship



There was a slight trend in the placebo-adjusted change from baseline PRA, aldosterone and angiotensin II (see figures 17, 18, and 19).

Figure 17

PK/PD relationship for plasma renin activity

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma renin activity (ng/mL/hr) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

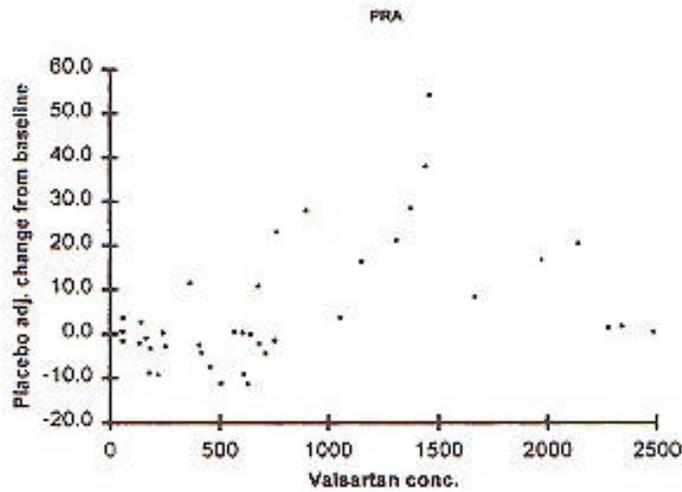


Figure 18

PK/PD relationship for plasma aldosterone concentration

Plot of plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

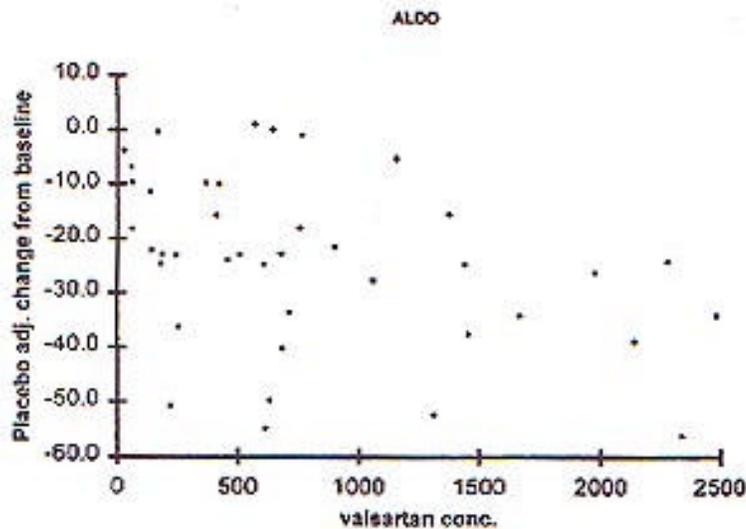
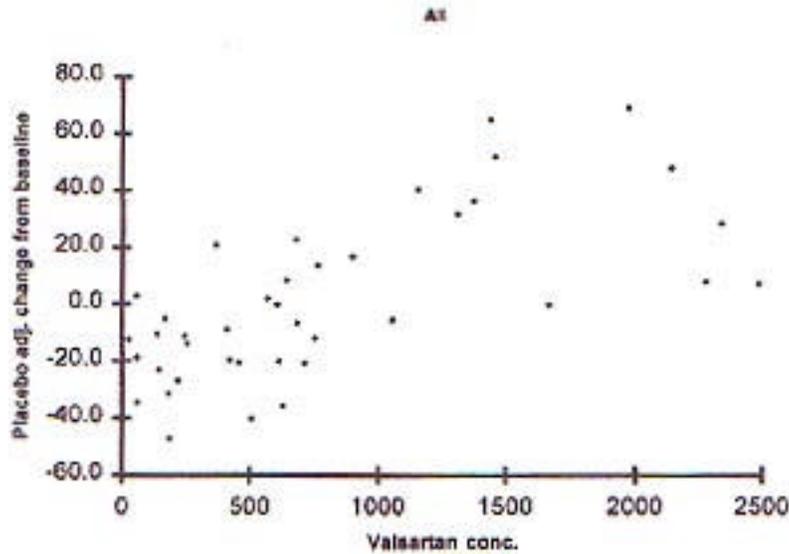


Figure 19

PK/PD relationship for plasma angiotensin II concentration

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.



Safety

There were no premature discontinuations after randomization. There were no deaths during this trial. Out of 25 randomized patients, 10 (8 on valsartan, 2 on placebo) reported adverse experiences.

There was one serious adverse experience (deterioration in CHF). A 65 year old 81 kg male with Class III CHF, randomized to valsartan 160 mg, was admitted to the CCU, 24 hours after dosing with trial medication, for IV infusions of dopamine (2mcg/kg/min) and dobutamine (10 mcg/kg/min). After 27 days, the patient was discharged with adjusted medications.

Table 7. Treatment-emergent adverse experiences (occurring in at least 2 patients on valsartan)

(all randomized patients)

Adverse event by primary term	Placebo (n=4) n (%)	Total valsartan (n=21) n (%)
Deterioration of basic disease	0	2 (9.5)
Dizziness	0	3 (14.5)

Source: Volume 12, Table 9.1:5

For further discussion, including evaluation of laboratory results, please see the Integrated Summary of Safety.

Medical Reviewer's Comments:

This was a small, single-dose open-label study investigating hemodynamic and pharmacokinetic effects with valsartan compared to placebo. The small sample size, as well as baseline differences between the treatment groups, limit interpretation of the data. No dose-response pattern could be seen in reviewing the hemodynamic data.

PK Reviewer's Comments:

Valsartan exhibits linear pharmacokinetics over the concentration range of 5-2,500 ng/mL. However, the data are highly variable. The linearity is consistent with previous reports in healthy volunteers. T_{max}, ~3 hours, is also similar to previous reports. T_{1/2} seems to be longer in patients with CHF than in healthy volunteers (median of ~9 hours compared to ~6 hours, respectively.) However, only two plasma samples were taken after 10 hours in this single dose study, so the T_{1/2} may be inaccurate.

There was a weak trend towards an increase in placebo adjusted mean change from baseline for PRA and Ang II, and a decrease in aldosterone concentrations with increasing valsartan concentrations. However, no definitive conclusions regarding these trends can be made from this study.

Medical Reviewer's Conclusions:

No efficacy conclusions will be drawn given the limited data. Valsartan appeared to be well tolerated in this study.

PK Reviewer's Conclusions :

Valsartan exhibits 2-compartment linear pharmacokinetics over the concentration range of 5 to 2,500 ng/mL (doses of 10 mg to 160 mg).

Single doses of valsartan in this small patient study do not show an apparent concentration response relationship with respect to PCWP and CO.

An open-label, two phase, four period, multiple dose study to assess the pharmacokinetics of valsartan in patients with congestive heart failure

PROTOCOL: 105
VOLUME: 9 and 10
PAGES: 6-1 to 6-258

PRINCIPAL INVESTIGATOR: Jon Ruckel, MD
CLINICAL LABORATORY: Northwest Kinetics, Tacoma WA
CITATION: not applicable
TRIAL PERIOD: August 2, 1997 to November 6, 1997

OBJECTIVES:

- Primary: Determine the steady state pharmacokinetics of twice daily valsartan in patients with CHF (NYHA class II or III).
- Secondary: Determine single dose pharmacokinetics of valsartan in patients with CHF (NYHA class II or III).
- Secondary: Assess the tolerability of twice daily valsartan in patients with CHF.

STUDY DESIGN: open label, two-phase, four period single and multiple dose study

DURATION: Approximately 25 days.

POPULATION: Eighteen out of 20 enrolled chronic stable (1 month) CHF patients with NYHA Class II or III completed the study. Patients had to have an EF ≤ 40% as determined by a MUGA or ECHO. All patients were between the ages of 18 – 75 years.

PROCEDURE: The procedures are as outlined in Table 1.

Table 1. Procedures

Period	Day[*]	Visit	Treatment^{**}	Valsartan Cp
Screening	-21 to -2	1	-	
Baseline	-1	2	-	
Phase I	1	3	40, 80 or 160 mg	Day 1: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr post dose
Phase II, Period 1	2-8	4-5	40 q 12h x 7 d	Day 7: trough Day 8: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose
Phase II, Period 2	9-15	6	80 q 12h x 7 d	Day 14: trough Day 15: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose
Phase II, Period 3	16-22	7	160 mg q 12h x 7 d	Day 21: trough Day 22: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose

* relative to dose 1 given on Day 1

** Subjects fasted for 10 hours prior to dosing on Day 1, the nights of Day 7, 14, and 21, and for 4 hours after dosing on Day 1, 8, 15, and 22.

Safety evaluations occurred as specified times during each treatment period and included physical exams, vital signs and adverse event monitoring.

Other medications

Patients on standard therapy for CHF were required to be on stable doses for at least 4 weeks prior to the baseline period.

Drug supply

The study drug was provided by Novartis, Suffern, NY. All patients were instructed to swallow the medication whole at 8 am and 8 pm with 200 mL of water.

Table 2. Batch and formulation for valsartan

Treatment	Dose	Batch No.	Formulation No.
Valsartan	40 mg capsule	E-15918R1	H-4030
	80 mg capsule	E-15866	H-4031
	160 mg capsule	E-15920	H-4032

ASSAY: Plasma valsartan concentrations were determined by a validated HPLC method. The assay was suitable for analyzing valsartan (See Table 3).

Table 3. Assay Quality

	Precision (CV %)	Accuracy (%)	Sensitivity (ng/mL)	Linearity (ng/mL)
Valsartan	< 11%	Within 2.5	5.0 – 5,000	≥ 0.9307

ANALYSIS :

Pharmacokinetics

Single dose - Tmax, T ½, Cmax, AUC₀₋₂₄, and AUC₀₋₄ were determined for each dose.

Multiple dose - τ, Tmax, Cmin, AUC_τ, apparent CL/wt, accumulation factor (Cmax of multiple dose/Cmax of single dose), and fluctuation index (Cmax-Cmin/Caverage, where Caverage is AUC_τ/12) were determined for each dose.

Clearance was evaluated between two age groups (< 65 years and > 65 years).

The sponsor assessed dose proportionality based on β determined from fitting Cmax and AUC parameters vs. dose to a power model (P=α*dose^β). Dose proportionality was evaluated for AUC₀₋₂₄, AUC₀₋₄ and Cmax for the single dose and AUC_τ and Cmax for multiple dose.

Statistics

Two sample t-tests were performed to compare age groups (≤ 65 years old and > 65 years old) for AUC and clearance (adjusted to body weight), and to examine if there was an age dependent effect on the AUC and clearance of valsartan in the patients studied.

RESULTS: Eighteen of twenty patients completed the trial. One discontinued because she developed renal insufficiency and the other discontinued because he developed PSVT.

Table 4. Demographics

	Mean (SD)	Range
Race (W/B)	15/3	
Males/Females	14/4	
Age (yr)	63.1 (10.1)	43-79
Ejection fraction (%)	27.9 (6.8)	18-39
Weight (kg)	90.7 (20.5)	71-140
Height (cm)	172.2 (10.7)	150-187

PHARMACOKINETIC RESULTS: Valsartan exhibits a 2-compartment body model as can be seen from the plasma concentration time curves for single and multiple dose in Figures 1 and 2, respectively.

Figure 1. Valsartan concentrations after single dose for three doses

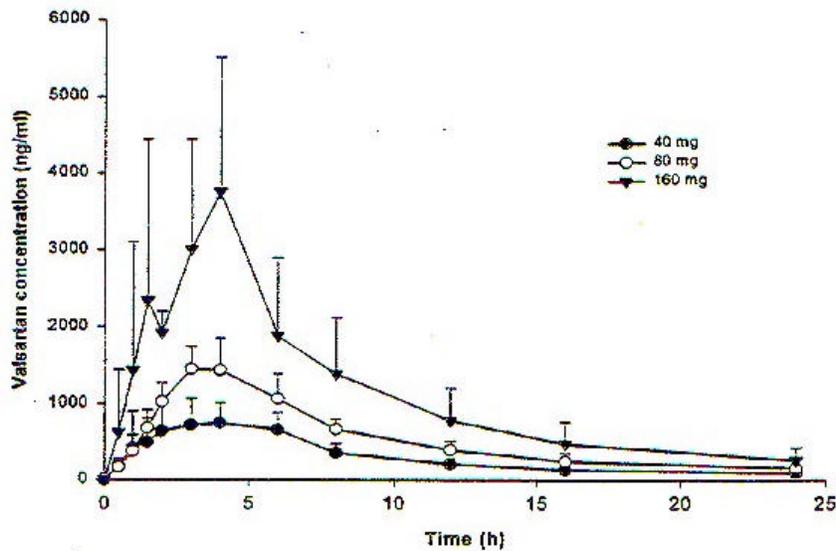
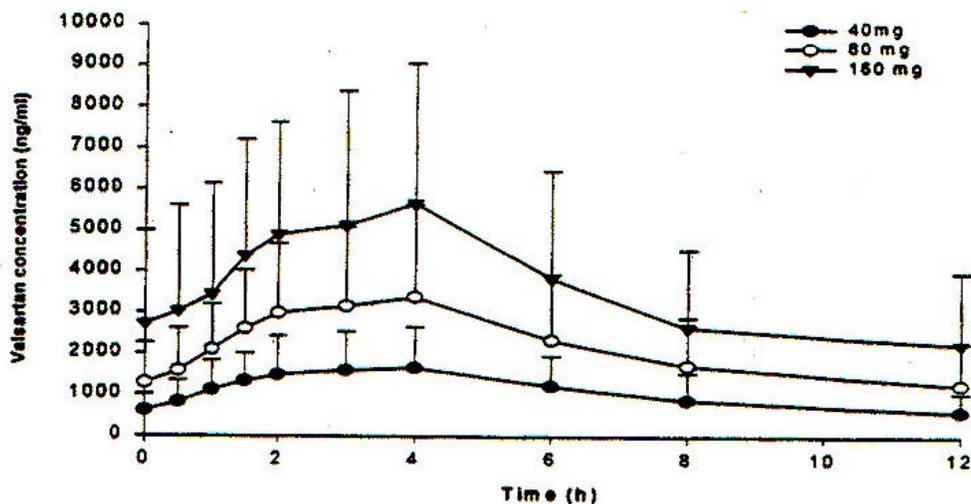


Figure 2. Valsartan concentrations at steady state for three doses



Pharmacokinetic parameters from single and multiple dose are shown in Table 5 and 6, respectively. T_{max} is attained in ~3 hours. T_{1/2} is ~ 6.5 hours. There is high variability in C_{max} and AUC after both single and multiple doses. The mean AUC after multiple dose was more than 50% higher than after single dose, although there was some overlap in AUCs.

Table 5. Mean (SD) PK parameters after single dose valsartan in CHF patients

n	Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)*	AUC ₍₀₋₂₄₎ (ng*hr/mL)	AUC ₀₋₄ (ng*hr/mL)	T _{1/2} (hr)
4	40	870 (304)	4	7296 (2497)	8363 (2969)	6.8 (0.9)
5	80	1560 (336)	4	12811 (1903)	13449 (2089)	5.7 (0.2)
6	160	4209 (2045)	3.5	27832 (12264)	30099 (13539)	6.5 (2.0)

* median

The fluctuation index was ~1.4 across all doses. C_{max} after multiple dose is higher than after single dose, suggesting accumulation. The accumulation factor was similar except for the 80 mg dose. The higher value observed for the 80 mg dose could be due to one patient who had an accumulation factor of 6.9. This subject had the lowest C_{max} after the first 80 mg dose.

Table 6. Mean (SD) steady state valsartan pharmacokinetics in 18 CHF patients

Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)*	AUC ₍₀₋₁₂₎ (ng*hr/mL)	T _{1/2} (hr)	Accumulation factor
40	1940 (971)	3	13119 (7220)	5.2 (1.9)	1.6 (0.5)
80	3951 (2290)	2.5	25936 (15670)	6.5 (2.4)	2.7 (2.1)
160	6403 (3190)	2.0	43540 (25897)	6.6 (3.9)	1.7 (0.4)

* median

The sponsor's fit of the steady state AUC and C_{max} data estimated a β of 0.85 and 0.86, respectively, suggesting that valsartan exhibits linear pharmacokinetics with multiple dose (see Table 7). The fit for single dose also suggest dose proportionality.

Table 7. Summary of model parameter estimates

	Single dose				Multiple dose			
	C _{max} (ng/mL)		AUC ₀₋₂₄ (ng*hr/mL)		C _{max} (ng/mL)		AUC ₀₋₁₂ (ng*hr/mL)	
	ln a	b	ln a	b	ln a	b	ln a	b
Mean	2.64	1.09	5.43	0.92	4.3	0.86	6.24	0.85
SE (%)	68	15	62	14	33	7	28	6
90% CI	0.83, 1.36		0.67, 1.17		0.74, 0.98		0.75, 0.95	

CI = confidence interval

Figures 3 to 6 show the mean (SD) data that also supports the linearity with single and multiple doses.

Figure 3. Mean (SD) valsartan AUCs following single doses of 40, 80 and 160 mg in CHF patients

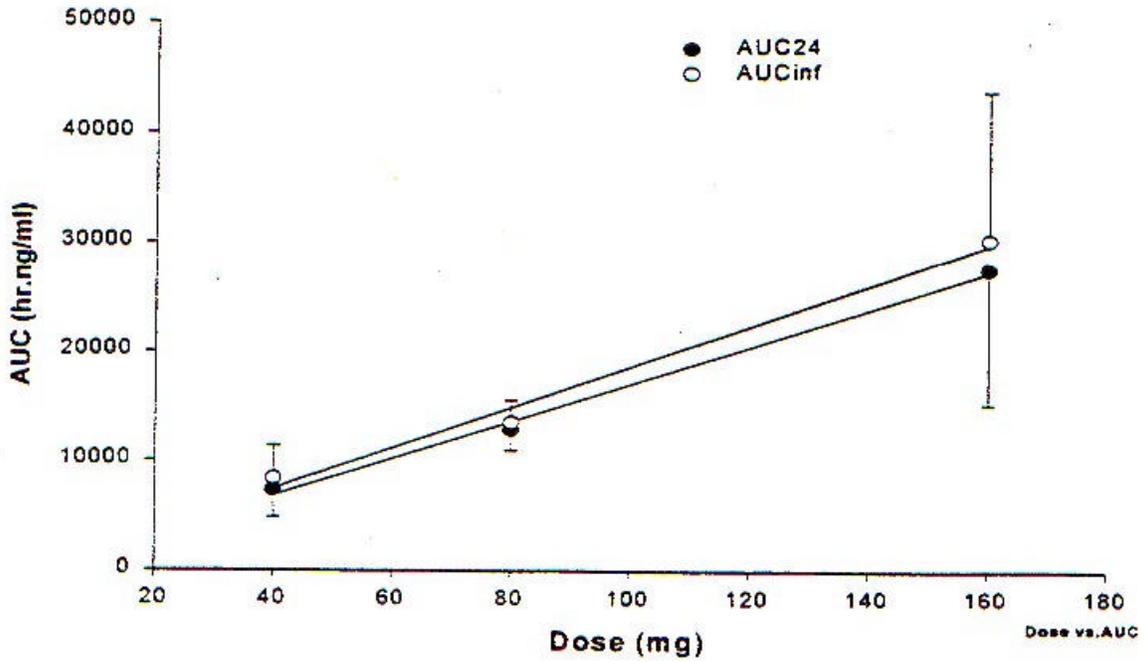


Figure 4. Mean (SD) C_{max} following single doses of 40, 80 and 160 mg in CHF patients

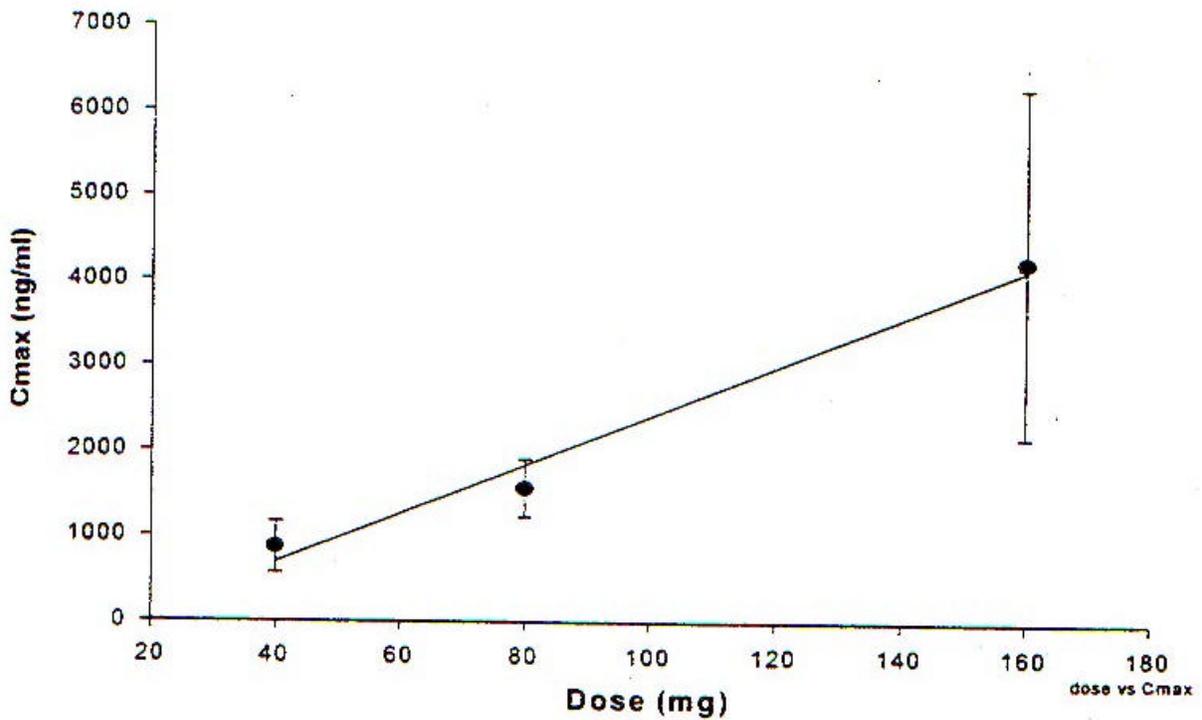


Figure 5. Mean (SD) valsartan AUC_{0-12} following multiple doses of 40, 80 and 160 mg in CHF patients

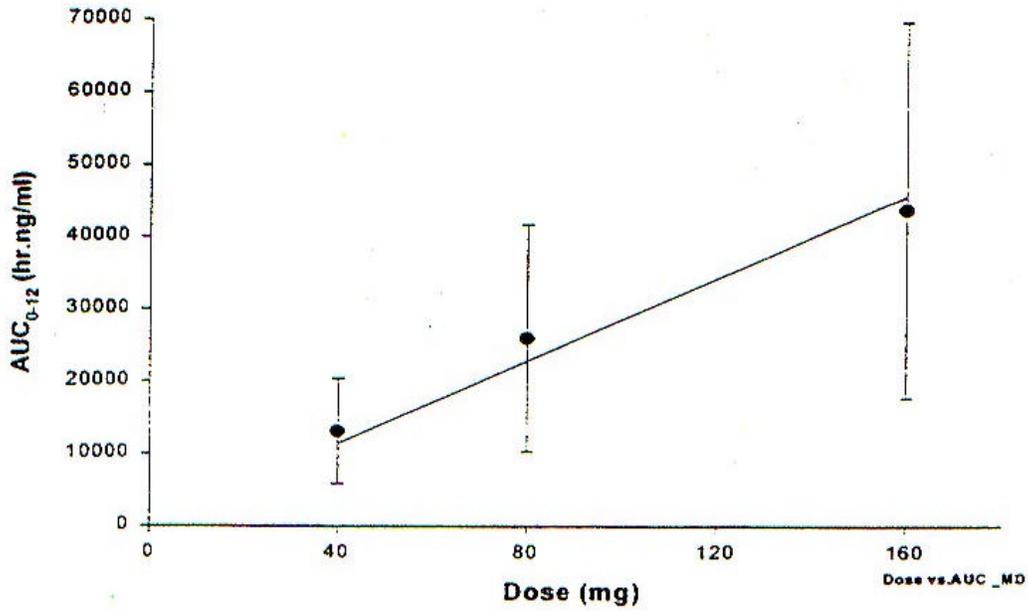
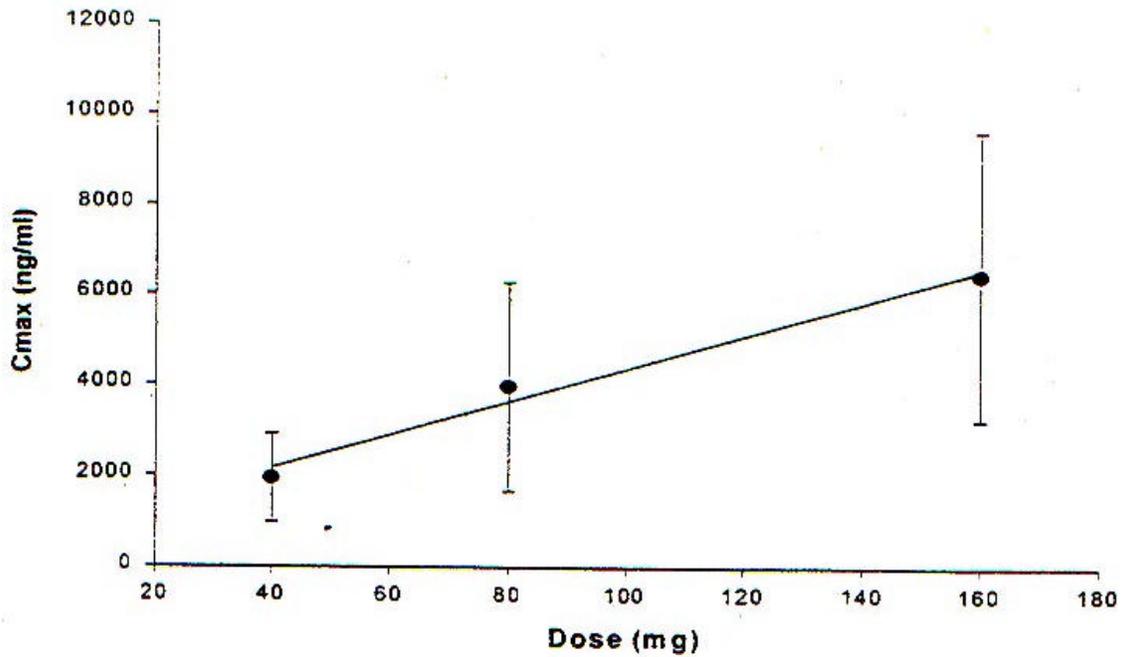


Figure 6. Mean (SD) valsartan C_{max} following multiple doses of 40, 80 and 160 mg in CHF patients



Clearance of valsartan was ~ 10-20% lower in nine patients aged ≤ 65 years old compared to nine patients > 65 years old. There was no statistically significant difference between the two groups. Additionally, there was considerable variability (~50%) resulting in overlap in clearances (see Table 8 and Figure 7).

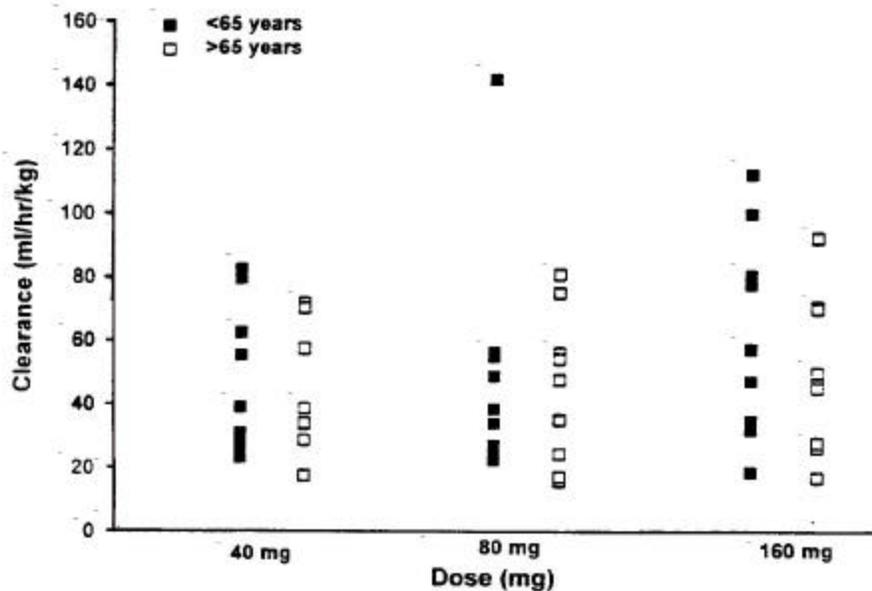
Table 8. Clearance (mL/hr/kg)* of young and elderly patients with CHF

Dose (mg)	≤ 65 years old	> 65 years old
40	47.4 (23.1)	41.0 (20.7)
80	49.7 (36.7)	45.1 (23.8)
160	62.1 (32.1)	49.4 (24.4)

* mean (SD)

Figure seven shows the large variability in clearance between patients ≤ 65 years old and patients > 65 years old.

Figure 7. Comparison of clearance by age in patients with CHF



SAFETY RESULTS: Eighteen of twenty patients reported adverse experiences in this study. Most A/E's were rated as mild to moderate by the investigator. The most common A/E were dizziness (n=11), hypotension (n=7), headache (n=5), dyspnea (n=5), fatigue (n=3), leg edema (n=3), viral infection (n=3) and coughing (n=3). The investigator did not deem these experiences to be dose related. There were no clinically significant adverse laboratory results or vital sign measurements.

REVIEWER'S COMMENTS:

Table 9. Pharmacokinetic comparison between healthy volunteers and patients with CHF

Similarities
Linear pharmacokinetics
T _{max} in ~3 hours
T _{1/2} is ~6.5 hours
Reduced clearance in elderly
Differences
Accumulation factor of ~1.7 in CHF (vs. 1.3)
CL ~ 4.5 L/h in CHF (vs. 2.2 L/h) ¹
C _{max} and AUC ~ 1.3 – 2x higher in CHF

¹ After adjusting for systemic bioavailability of 23% for the capsule, clearance would be ~1.04 L/h, which is ~ 50% of that observed in healthy volunteers.

The apparent age effect is in agreement with results from previous studies.

CONCLUSIONS:

Valsartan exhibits linear pharmacokinetics with single and multiple doses in patients with CHF. T_{max} is ~3 hours and T_{1/2} is approximately 6.5 hours. Clearance is reduced by ~50% in patients with CHF compared to healthy volunteers. Valsartan clearance was ~ 10-20% lower in elderly patients with CHF compared to young patients with CHF. A twice daily dose accumulates by a factor of 1.7 compared to single dose.

Valsartan was well tolerated in this patient population.

Request for waiver for 40 mg tablet

Source: NDA 21-283 (SE1-001), submission date 7/23/01

SUMMARY:

Information to support a biowaiver for the 40 mg tablet:

- Compositionally proportional (see Table 1)
- Linear pharmacokinetics (study 102 and 105 included in this review)
- Similar in vitro dissolution profiles in three media

BACKGROUND:

In the clinical trials for CHF, hard gelatin capsules were used.

The sponsor has demonstrated bioequivalence between two 160 mg capsules and the 320 mg tablets. A BE waiver for the 80 mg and 160 mg tablets was recently granted. The approved dissolution method and specifications for the 80 mg, 160 mg and 320 mg tablets are:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C

Apparatus: USP II (paddle)

Speed: 50 rpm

Specifications: Q = [] in 30 minutes

REVIEW :

- Compositionally proportional

Table 1. Composition of Diovan 40, 80, 160 and 320 mg film-coated tablets

Ingredient	Amount per tablet (mg)				Function	Reference to standard
	40	80	160	320		
Valsartan	40.00	80.0	160.0	320.0	Active ingredient	Novartis monograph
Microcrystalline cellulose	[]	NF
Crospovidone	[]	NF
Colloidal anhydrous silica/ colloidal silicon dioxide	[]	NF
Magnesium stearate	[]	NF
Core weight	[]	
Coating						
Coating premix ¹	[]	Novartis monograph
Purified water ²	[]	USP
Total tablet weight	80.30	161.0	319.0	636.0		

¹ The coating premixes are commercially available products composed as given in the table below.

² removed during processing

- Dissolution

The dissolution data for the 40 mg tablet was generated on Batch # x 226 0799 in 3 media using 1000 mL.

Table 2. Individual dissolution results using a paddle

Batch Dosage strength	Medium Speed	Time (min)
X226 0799 40 mg	pH 6.8 50 rpm	10
		20
		30
		45
X226 0799 40 mg	pH 4.5 50 rpm	10
		20
		30
		45
		60
		90
X226 0799 40 mg	pH 4.5 75 rpm	15
		30
		60
		120
X226 0799 40 mg	pH 1.0 75 rpm	15
		30
		60
		120

X226 0799 40 mg	pH 1.0 50 rpm	10	0.4, 0.1, 0.1, 0.3, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1
		20	1.0, 0.7, 0.8, 0.5, 0.8, 0.6, 2.5, 0.8, 0.8, 0.6, 0.6
		30	4.1, 2.6, 3.3, 2.4, 3.0, 2.8, 5.3, 3.3, 3.3, 2.5, 2.4, 2.6
		45	6.7, 4.3, 5.2, 4.0, 4.8, 4.6, 7.3, 5.4, 5.4, 4.4, 5.1, 4.5

Table 3. Individual dissolution data for the 320 mg tablet in three media

Batch	Medium	Time	% dissolved
Dosage strength	Speed	(min.)	
X361 1199 320 mg	pH 4.5 75 rpm	15	98, 99, 100, 99, 98, 100, 101, 101, 101, 100, 101, 101
		30	100, 99, 100, 100, 99, 100, 102, 102, 101, 101, 102, 101
		60	100, 99, 101, 99, 99, 100, 102, 102, 101, 101, 102, 101
		120	102, 99, 101, 99, 99, 100, 102, 102, 101, 101, 102, 101
X361 1199 320 mg	pH 6.8 50 rpm	10	87, 88, 86, 85, 90, 91, 87, 88, 86, 85, 91, 87
		20	91, 92, 90, 89, 93, 94, 91, 92, 90, 91, 94, 90
		30	92, 94, 90, 90, 94, 95, 92, 93, 91, 92, 95, 91
		45	93, 95, 100, 91, 95, 95, 93, 94, 92, 93, 95, 93

	X361 1199 320 mg	pH 4.5 75 rpm	15
			30
			60
			120

Batch	Medium	Time	% dissolved
X361 1199 320 mg	pH 1.0 50 rpm	10	0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0
		20	1.1, 1.1, 1.1, 1.1, 1.1, 1.0, 1.2, 1.0, 1.1, 1.0
		30	3.0, 3.1, 3.1, 3.0, 3.1, 3.3, 2.9, 3.1, 3.1, 3.0, 3.0, 2.9
		45	4.3, 4.2, 4.3, 4.2, 4.3, 4.5, 4.0, 4.1, 4.3, 4.1, 4.1, 4.1

X361 1199 320 mg	pH 1.0 75 rpm	15
		30
		60
		120

These data were compared with in vivo data for the 320 mg tablet (Batch # x 361 1199) The F2 values calculated by the sponsor are shown in Table 2. The F2 value for the 40 mg tablet using the pH 6.8 buffer medium at 50 RPM was between 50 and 100.

Table 3. Dissolution and F2 for the 40 mg tablet in different media

Medium	Speed	F2
0.1 N HCl	75	70
pH 6.8 buffer	50	52
pH 4.5 buffer	50	36
pH 4.5 buffer	75	54

REVIEWER'S COMMENTS:

The sponsor does not specify the type of media used in the dissolution testing of the 40 mg tablet. After discussion with Robert Clark, from Novartis, on August 25, 2001, it was determined that the medium used was the same as the approved medium.

The sponsor did not need to calculate F2 at 15 minutes for the dissolution in pH 6.8, 50 rpm since more than [] was dissolved by 15 minutes.

The comparison of the dissolution between the 40 mg and 320 mg tablet at pH 4.5, 50 rpm failed. This is most likely because at pH 4.5, valsartan is not very soluble. Thus, it will take longer for a larger amount to dissolve (320 mg) compared to a smaller amount (40 mg). This difference in dissolution is not expected to result in differences in bioavailability in vivo.

CONCLUSION:

A bioequivalence waiver is granted for the 40 mg tablet and the specifications should be the same as what was previously approved.

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C

Apparatus: USP II (paddle)

Speed: 50 rpm

Specifications: Q = [] in 30 minutes

APPENDIX II: FORMULATION

The formulation was similar in all studies. For composition see page 27 of the review.

Table 1. Formulations and batch numbers of valsartan

Protocol No	Strength (mg)	Formulation No.	Batch No.	
Pharmacokinetic studies				
102	10	H-3573	1053/1	
	20	H-3574	1050/2	
	40	H-3575	1051/3	
	80	H-3576	1052/2	
	160	H-3577	1059/3	
105	40	H-4030	E-15918R1	
	80	H-4031	E-15866	
	160	H-4032	E-15920	
Pivotal Clinical Study				
107	40	H-4030	B970038	
			B970089 ^c	
			B980162 ^c	
			E-15865	
			E-15918R1	
			H-5040	
			H-5064	
	80		H-4031	B970046 ^c
				B970086 ^c
		B980013 ^c		
		B980014 ^c		
		B980034 ^c		
		E-15866 ^a		
		X066 0399 ^c		
	160	H-4032	B970043 ^c	
			B970044 ^c	
			B970088 ^c	
			B980002 ^c	
			B980035 ^c	
			B980068 ^c	
			B980069 ^c	
			B980075 ^c	
			B980166 ^c	
			B980172 ^c	
			E 39/98 ^c	
			E-15867 ^b	
			E-15920 ^b	
			H-5038 ^b	
			H-5066 ^b	

^a compared to the final market image (capsule formulation currently marketed), capsule content is identical and capsule shell and size differ.

^b compared to the final market image (capsule formulation currently marketed), capsule content is identical and capsule shell is slightly different.

^c Site of clinical supply manufacture and packaging different than the rest because of the merger of Ciba Pharmaceuticals and Sandoz Pharmaceuticals Corporation.

APPENDIX III: Sponsor's proposed package insert

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.

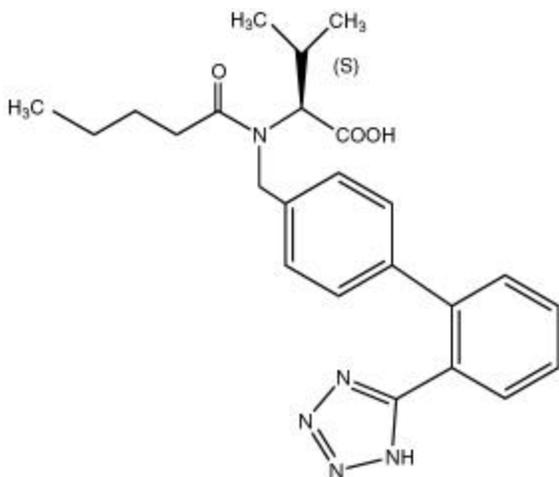
When pregnancy is detected, Diovan should be discontinued as soon as possible.

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, croscopovidone, 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.ⁱ 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.

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.ⁱⁱ

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

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: Hemodynamics and Neurohormones. Hemodynamics and plasma neurohormones were measured in NYHA class II-IV heart failure patients with pulmonary

capillary wedge pressure ≥ 15 mmHg in 2 short term, chronic therapy studies. In one study, which included patients chronically treated with ACE inhibitors, single and multiple doses of valsartan given in combination with an ACE inhibitor improved hemodynamics including pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and systolic blood pressure (SBP). Reductions were observed in plasma aldosterone (PA) and plasma norepinephrine (PNE) levels after 28 days of treatment.ⁱⁱⁱ In the second study, which included only patients untreated with ACE inhibitors for at least 6 months prior to enrollment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment.^{iv} In the long-term Valsartan Heart Failure Trial (Val-HeFT), plasma norepinephrine and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.^v

Morbidity and mortality. The Valsartan Heart Failure Trial was a randomized, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF $< 40\%$ and left ventricular internal diastolic diameter (LVIDD) > 2.9 cm/m². The study enrolled 5010 patients in 16 countries who were randomized to receive either valsartan or placebo in addition to all other appropriate therapy including ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan in the Valsartan Heart Failure Trial was 254 mg. The study had 2 primary endpoints: all cause mortality (time to death) and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. All cause mortality was similar in the valsartan and placebo groups. Morbidity was significantly reduced by 13.2% with valsartan compared with placebo. The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalization. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. However, risk ratios favoring placebo were observed for those patients treated with the combination of a beta-blocker, an ACE inhibitor and valsartan.^v Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Exercise tolerance and capacity. The effects of valsartan in addition to usual heart failure therapy on exercise tolerance using the Modified Naughton Protocol were measured in NYHA class II-IV heart failure patients with left ventricular dysfunction (LVEF $\leq 40\%$). Increased exercise time from baseline was observed for all treatment groups. Greater mean increases from baseline in exercise time were observed for the valsartan groups compared to the placebo group, although statistical significance was not achieved. The greatest improvements were observed in the subgroup of patients not receiving ACE inhibitor therapy where mean changes in exercise time were 2 times greater for the valsartan groups compared to the placebo group.^{vi} The effects of valsartan compared to enalapril on exercise capacity using the six minute walk test were determined in NYHA class II and III heart failure patients with left ventricular ejection fraction $\leq 45\%$ who had been receiving ACE inhibitor therapy for at least 3 months prior to study entry. Valsartan 80 mg to 160 mg once daily was at least as effective as enalapril 5 mg to 10 mg twice daily, with respect to exercise capacity, as measured by the six minute walk test in patients previously stabilized on ACE inhibitors and directly switched to valsartan or enalapril.^{vii}

NYHA class, Signs and symptoms, Quality of life, Ejection fraction. In the Valsartan Heart Failure Trial, valsartan treated patients showed significant improvement in NYHA class, and

heart failure signs and symptoms, including dyspnea, fatigue, edema and rales compared to placebo. Patients on valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVDD significantly reduced from baseline at endpoint compared to placebo.^{v,vi}

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 receiving usual therapy such as diuretics, digitalis and either ACE inhibitors or beta-blockers; presence of all these standard therapies is not mandatory.

In these patients, Diovan improves morbidity, primarily via reduction in hospitalization for heart failure. Diovan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see 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/m^2 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

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. Caution should be observed when initiating therapy in patients with heart failure. In controlled trials, the incidence of hypotension in valsartan treated patients was 5.5% compared to 1.8% in placebo treated patients.^{viii}

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, especially when Diovan has been given concomitantly with a diuretic, and 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. Evaluation of patients with heart failure should always include assessment of 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.

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/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.^v

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), 9.9% of valsartan patients discontinued for adverse events vs. 7.3% of placebo patients.^{ix}

Table 1 shows drug related 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.

	Table 1	
	Valsartan (n=3282)	Placebo (n=2740)

Dizziness (excluding vertigo)	13.1%	5.8%
Hypotension, not otherwise specified	5.5%	1.8%
Dizziness, postural	2.2%	0.9%

Other drug related adverse events with an incidence greater than 1% and greater than placebo included postural hypotension, fatigue, diarrhea NOS, headache NOS, nausea, renal impairment NOS, hyperkalemia and vertigo. (NOS = not otherwise specified).^{viii}

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

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.^x

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. 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.

HOW SUPPLIED

Diovan® (valsartan) is available as capsules containing valsartan 80 mg or 160 mg. Both strengths are packaged in bottles of 100 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

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

Unit Dose (blister pack) NDC 0083-4001-61

Box of 100 (strips of 10)

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).

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REV: CHF NDA Printed in U.S.A.
23-May-01 13:30 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.

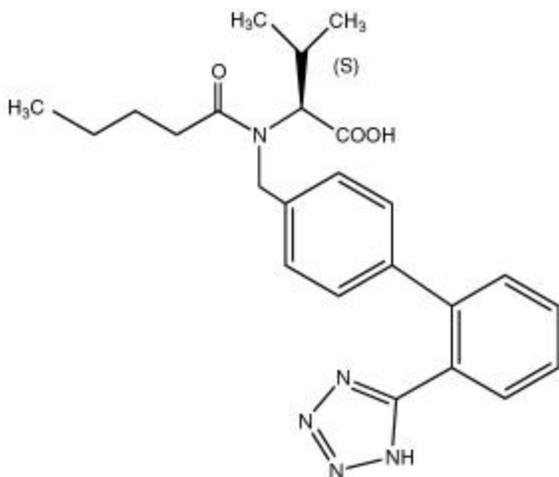
When pregnancy is detected, Diovan should be discontinued as soon as possible.

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.^{xi} 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.

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.^{xiii}

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

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: Hemodynamics and Neurohormones. Hemodynamics and plasma neurohormones were measured in NYHA class II-IV heart failure patients with pulmonary

capillary wedge pressure ≥ 15 mmHg in 2 short term, chronic therapy studies. In one study, which included patients chronically treated with ACE inhibitors, single and multiple doses of valsartan given in combination with an ACE inhibitor improved hemodynamics including pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and systolic blood pressure (SBP). Reductions were observed in plasma aldosterone (PA) and plasma norepinephrine (PNE) levels after 28 days of treatment.^{xiii} In the second study, which included only patients untreated with ACE inhibitors for at least 6 months prior to enrollment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment.^{xiv} In the long-term Valsartan Heart Failure Trial (Val-HeFT), plasma norepinephrine and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.^{xv}

Morbidity and mortality. The Valsartan Heart Failure Trial was a randomized, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF $< 40\%$ and left ventricular internal diastolic diameter (LVIDD) > 2.9 cm/m². The study enrolled 5010 patients in 16 countries who were randomized to receive either valsartan or placebo in addition to all other appropriate therapy including ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan in the Valsartan Heart Failure Trial was 254 mg. The study had 2 primary endpoints: all cause mortality (time to death) and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. All cause mortality was similar in the valsartan and placebo groups. Morbidity was significantly reduced by 13.2% with valsartan compared with placebo. The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalization. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. However, risk ratios favoring placebo were observed for those patients treated with the combination of a beta-blocker, an ACE inhibitor and valsartan.^v Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Exercise tolerance and capacity. The effects of valsartan in addition to usual heart failure therapy on exercise tolerance using the Modified Naughton Protocol were measured in NYHA class II-IV heart failure patients with left ventricular dysfunction (LVEF $\leq 40\%$). Increased exercise time from baseline was observed for all treatment groups. Greater mean increases from baseline in exercise time were observed for the valsartan groups compared to the placebo group, although statistical significance was not achieved. The greatest improvements were observed in the subgroup of patients not receiving ACE inhibitor therapy where mean changes in exercise time were 2 times greater for the valsartan groups compared to the placebo group.^{xvi} The effects of valsartan compared to enalapril on exercise capacity using the six minute walk test were determined in NYHA class II and III heart failure patients with left ventricular ejection fraction $\leq 45\%$ who had been receiving ACE inhibitor therapy for at least 3 months prior to study entry. Valsartan 80 mg to 160 mg once daily was at least as effective as enalapril 5 mg to 10 mg twice daily, with respect to exercise capacity, as measured by the six minute walk test in patients previously stabilized on ACE inhibitors and directly switched to valsartan or enalapril.^{xvii}

NYHA class, Signs and symptoms, Quality of life, Ejection fraction. In the Valsartan Heart Failure Trial, valsartan treated patients showed significant improvement in NYHA class, and

heart failure signs and symptoms, including dyspnea, fatigue, edema and rales compared to placebo. Patients on valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVDD significantly reduced from baseline at endpoint compared to placebo.^{v,vi}

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 receiving usual therapy such as diuretics, digitalis and either ACE inhibitors or beta-blockers; presence of all these standard therapies is not mandatory.

In these patients, Diovan improves morbidity, primarily via reduction in hospitalization for heart failure. Diovan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see 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/m^2 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

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. Caution should be observed when initiating therapy in patients with heart failure. In controlled trials, the incidence of hypotension in valsartan treated patients was 5.5% compared to 1.8% in placebo treated patients.^{xviii}

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, especially when Diovan has been given concomitantly with a diuretic, and 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. Evaluation of patients with heart failure should always include assessment of 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.

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/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.^v

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), 9.9% of valsartan patients discontinued for adverse events vs. 7.3% of placebo patients.^{xix}

Table 1 shows drug related 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.

	Table 1	
	Valsartan (n=3282)	Placebo (n=2740)

Dizziness (excluding vertigo)	13.1%	5.8%
Hypotension, not otherwise specified	5.5%	1.8%
Dizziness, postural	2.2%	0.9%

Other drug related adverse events with an incidence greater than 1% and greater than placebo included postural hypotension, fatigue, diarrhea NOS, headache NOS, nausea, renal impairment NOS, hyperkalemia and vertigo. (NOS = not otherwise specified).^{viii}

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

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.^{xx}

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. 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.

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 of 30 tablets, 90 tablets or 100 tablets and unit dose blister packages. Tablets are debossed as follows:

40 mg Tablet – Yellow, round, non-scored, slightly convex with bevelled edges, debossed with DO on one side and NVR on the other.

Bottles of 30 NDC 0078-0376-15

Bottles of 90 NDC 0078-0376-34

Bottles of 100 NDC 0078-0376-05

Unit Dose (blister pack) NDC 0078-0376-06

Box of 100 (strips of 10)

80 mg Tablet - Pale red, almond-shaped with bevelled edges, debossed with DV on one side and NVR on the other.

Bottles of 30 NDC 0078-0358-15

Bottles of 90 NDC 0078-0358-34

Bottles of 100 NDC 0078-0358-05
Unit Dose (blister pack) NDC 0078-0358-06
Box of 100 (strips of 10)

160 mg Tablet - Grey-orange, almond-shaped with bevelled edges, debossed with DX on one side and NVR on the other.

Bottles of 30 NDC 0078-0359-15
Bottles of 90 NDC 0078-0359-34
Bottles of 100 NDC 0078-0359-05
Unit Dose (blister pack) NDC 0078-0359-06
Box of 100 (strips of 10)

320 mg Tablet – Dark greyish violet, almond-shaped with bevelled edges, debossed with DXL on one side and NVR on the other.

Bottles of 30 NDC 0078-0360-15

Bottles of 90 NDC 0078-0360-34
Bottles of 100 NDC 0078-0360-05
Unit Dose (blister pack) NDC 0078-0360-06
Box of 100 (strips of 10)

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).

PI - CHF Proposed40mgV2.doc

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

8-Jun-01 13:55 Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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Endnotes for Sponsor's Proposed Package Insert

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- ⁱ [Nonclinical Pharmacology Section, Literature reference L21: J Hypertens 1998;16:843-852](#)
- ⁱⁱ [Human Pharmacokinetics and Bioavailability Section, Protocol 105](#)
- ⁱⁱⁱ [Clinical Data Section, Protocol 104](#)
- ^{iv} [Clinical Data Section, Protocol 103](#)
- ^v [Clinical Data Section, Protocol 107](#)
- ^{vi} [Clinical Data Section, Protocol 106](#)
- ^{vii} [Clinical Data Section, Protocol 110](#)
- ^{viii} [Clinical Data Section, ISS, Table 5-9](#)
- ^{ix} [Clinical Data Section, ISS, Table 5-16](#)
- ^x [Clinical Data Section, ISS, Table 6-7](#)
- ^{xi} [Nonclinical Pharmacology Section, Literature reference L21: J Hypertens 1998;16:843-852 - NDA 20-665 S-016 Vol 6, Page 5-177](#)
- ^{xii} [Human Pharmacokinetics and Bioavailability Section, Protocol 105 - NDA 20-665 S-016 Vol 9, Page 6-1](#)
- ^{xiii} [Clinical Data Section, Protocol 104 - NDA 20-665 S-016 Vol 14, Page 8-2](#)
- ^{xiv} [Clinical Data Section, Protocol 103 - NDA 20-665 S-016 Vol 65, Page 8-1](#)
- ^{xv} [Clinical Data Section, Protocol 107 - NDA 20-665 S-016 Vol 28, Page 8-1](#)
- ^{xvi} [Clinical Data Section, Protocol 106 - NDA 20-665 S-016 Vol 20, Page 8-1](#)
- ^{xvii} [Clinical Data Section, Protocol 110 - NDA 20-665 S-016 Vol 72, Page 8-1](#)
- ^{xviii} [Clinical Data Section, ISS, Table 5-9 - NDA 20-665 S-016 Vol 77, Page 8-63](#)
- ^{xix} [Clinical Data Section, ISS, Table 5-16 - NDA 20-665 S-016 Vol 77, Page 8-70](#)
- ^{xx} [Clinical Data Section, ISS, Table 6-7 - NDA 20-665 S-016 Vol 77, Page 8-106](#)