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APPLICATION NUMBER

NDA 20-665/S-016

NDA 21-283/S-001

Medical Review(s)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review #2

NDA: 20-665/SE1-016
21-283/SE1-001

Sponsor: Novartis

Submission: In the Approvable letter of 24 October 2001, the sponsor was invited to submit a thorough analysis of findings pertaining to the population not on ACE inhibitor to support the hypothesis that valsartan was able to substitute for an ACE inhibitor. Retrospective analyses of these data are the subject of the sponsor's submissions of 28 November 2001 and, more fully, 22 January 2002.

Review date: 6 February 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 20-665

NDA 21-283

HFD-110/Project Manager

HFD-110/Stockbridge

The no-ACEI group averaged 4 years older, had more females, fewer minorities, a 6-month longer average history of heart failure, and a somewhat higher proportion of NYHA class III subjects. Otherwise, the baseline characteristics of the ACEI and no-ACEI sub-groups were similar in Val-HeFT.

As previously noted, primary end point effects were larger in the group not on ACE inhibitors, as shown in Table 1.

Table 1. Primary end points (% Val-HeFT)

	No ACEI				ACEI			
	Plac N=181	Val N=185	HR	P	Plac N=2318	Val N=2326	HR	P
Mortality	27	17	0.67	0.017	19	20	1.06	0.35
CV mortality	22	16	0.76	0.074	16	17	1.04	0.49
Morbidity	43	25	0.56	0.0002	31	29	0.90	0.10
Total non-fatal	27	13	0.46	0.0004	19	15	0.76	0.0003
CHF hosp	27	13	0.47	0.0006	18	14	0.76	0.0004

Thus, not only is the overall benefit in morbidity driven by the effects in the no-ACEI group, there is a likely mortality benefit manifest in the no-ACEI group, as well.

The sponsor's life table analyses show that effects on mortality and morbidity in the "No-ACE" group develop early and widen during the >2 years of follow-up, as shown in Figure 1.

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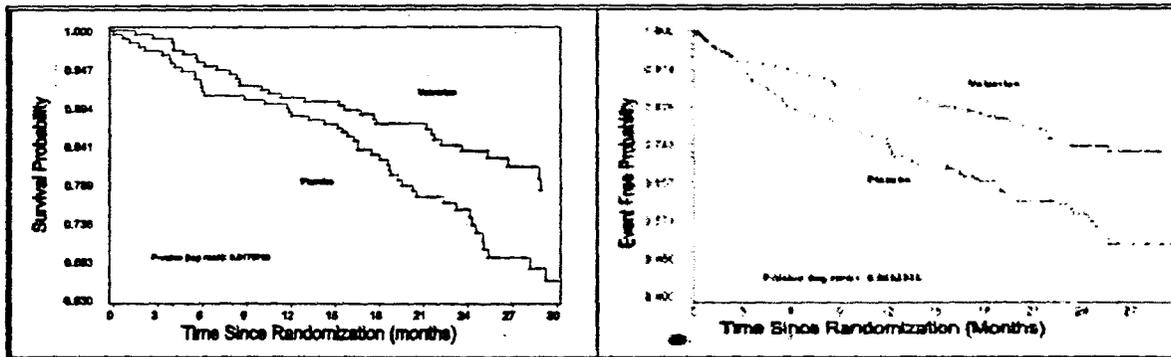


Figure 1. Mortality and morbidity in no-ACE subgroup (Val-HeFT)

Sponsor's analyses of Val-HeFT primary end points for the sub-group not receiving ACE inhibitors at baseline.

The sponsor also evaluated primary and secondary end points in population sub-groups defined by whether the subject was receiving a dose of ACE inhibitor at baseline that was above or below the median dose. These data are summarized in Table 2.

Table 2. Relative risk¹ by use of ACE inhibitors at baseline (Val-HeFT).

	Use of ACE inhibitors			
	None N=366	Low N=2035	Any N=4644	High N=2572
Mortality	0.67	0.99	1.06	1.15
Morbidity	0.56	0.86	0.90	0.96
Cardiovascular mortality	0.76	0.95	1.04	1.17
Non-fatal morbidity	0.46	0.73	0.76	0.79
Heart failure hospitalization	0.47	0.71	0.76	0.81
Total HF hospitalizations	0.43	0.72	0.81	0.92
Total non-HF hospitalizations	1.02	1.11	1.03	0.93
HF hospitalization days	0.30	0.66	0.78	0.90
Non-HF hospitalization days	1.00	1.11	1.03	0.97

For both primary end points (top two rows of Table 2), 3 pre-specified secondary end points (next 3 rows in table), and two other measures of hospitalizations for heart failure, for all of which there were apparent treatment effects in the no-ACEI sub-group, the treatment effect in the low-dose ACEI sub-group was of intermediate magnitude. There was no effect of treatment in the "No-ACE" sub-group for non-heart failure hospitalizations, and there was no apparent relationship to dose of ACE inhibitor.

Quality of life data (Minnesota Living with Heart Failure) were obtained in some countries. These data are consistent with a beneficial effect of valsartan in both ACEI and no-ACEI sub-groups, but the magnitude of the treatment effect (valsartan minus placebo) is more than twice as large in the no-ACEI group². The improvement in quality of life score was of intermediate magnitude in the sub-group receiving a low dose of ACE inhibitor. There was a similar trend of relatively improved quality of life score in the no-ACEI cohort of the exercise study 106.

LVEF and LVDD data are consistent with beneficial effects of valsartan in both ACEI and no-ACEI cohorts, but the magnitude of the treatment effect (valsartan minus

¹ Valsartan/placebo

² The overall nominal p-value is 0.005 by the sponsor's analysis. In the "No-ACE" subgroup, the p-value is 0.095.

placebo) is more than 3 times as large in the no-ACEI group. The reductions in norepinephrine and BNP levels were greater in the no-ACEI group.

The sponsor tabulated effects on various signs and symptoms of heart failure by the percentage of subjects who improved or worsened. As part of this review, the shift was assessed by the difference (percentage improved minus worsened) was calculated as a solitary indication of improvement, to compensate for any flattening of a distribution. Then the valsartan-minus-placebo difference was calculated as the overall treatment effect. Finally, the difference in treatment effect was taken between the no-ACEI and ACEI cohorts, to show if greater effects were seen in the no-ACEI cohort. The results are shown in Table 3.

Table 3. Effects on CHF signs and symptoms (Val-HeFT)

	Overall p-value	Effect favors	No-ACEI minus ACEI
Edema	0.003	Valsartan	15.0
Rales	0.001	Valsartan	11.8
Jugular venous distension	<0.001	Valsartan	5.4
Paroxysmal nocturnal dyspnea	0.001	Valsartan	4.9
Dyspnea at rest	0.029	Placebo	3.5
Orthopnea	0.11	Valsartan	-0.5
NYHA class	<0.001	Valsartan	-2.2
Fatigue	0.008	Valsartan	-3.6
Dyspnea on exertion	0.001	Valsartan	-4.5
Third heart sound	0.2	Valsartan	-4.8

Edema, rales, JVD, and PND all had robust effects overall, but larger effects in the no-ACEI cohort. There were overall effects on NYHA class, fatigue, and dyspnea on exertion, but somewhat larger effects in the ACEI cohort. Thus, there is no consistency with respect to CHF signs and symptoms by concomitant use of ACE inhibitors.

Six-minute walk was assessed in about 25% of subjects in Val-HeFT. Overall, there was no net effect (p=0.85), but there was a nominally significant (p=0.02) effect in the no-ACEI cohort of 35 subjects³ (+84 m in no-ACEI vs. -4 m on ACEI).

Treadmill exercise was evaluated in Study 106; there was no overall treatment effect (p=0.2-0.85 for various dose groups vs. placebo). In the cohort not receiving ACEI (about 14%), the effects were generally not nominally statistically significant, but the effects did favor active treatment (by 50 to 120 s) and the estimated effect sizes were larger than in the cohort receiving ACEI (-7 to 14 s).

The sponsor's response to the approvable letter answers the question posed as well as available data can. The results for Val-HeFT and the exercise tolerance study (106) are largely consistent with the hypothesis that valsartan can substitute for an ACE inhibitor in producing the ACE inhibitor's expected benefits in heart failure. These benefits include effects on mortality (chiefly cardiovascular), morbidity (chiefly heart failure hospitalizations), exercise tolerance (probably), ejection fraction, heart size, norepinephrine and BNP levels, and, perhaps, some of the signs and symptoms of heart failure. Consequently, valsartan should be approved for use in the population of heart failure patients intolerant of ACE inhibitors.

³ The sponsor's analyses assigned 0 distance to subjects who died or were unable to walk because of heart failure.

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/s/

Norman Stockbridge
2/6/02 06:24:10 AM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 20-665/SE1-016

21-283/SE1-001

Sponsor: Novartis

Submission: Efficacy supplement for the use of valsartan in the treatment of congestive heart failure.

Review date: 21 December 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Valsartan appears to be an effective treatment for CHF, reducing (at least) hospitalizations for heart failure. When and in whom it should be used is less clear.

Distribution: NDA 20-665

NDA 21-283

HFD-110/Project Manager

HFD-110/Stockbridge

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1 Background

The concept of the pivotal Val-HeFT study was discussed with the Agency in a teleconference in 1994 and an end-of-phase II meeting in 1996.

The sponsor has provided a financial disclosure statement, denying inappropriate financial arrangements as defined under 21 CFR 54.2(a), (b), or (f).

Valsartan is marketed in many other countries. The heart failure indication is under consideration in Europe.

Pediatric studies have not been performed.

This review is based upon the following documents: clinical pharmacology and biopharmaceutics reviews (Drs. Nhi and Targum), dated 10 September 2001; the combined medical-statistical review (Drs. Targum, Hung, and Karkowsky), dated 13 September 2001, and the chemistry and manufacturing reviews (Dr. Zimmerman), dated 11 October 2001. There is no pharmacology-toxicology review.

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2 Chemistry

Diovan is an approved product, available as capsules and tablets. The capsule formulation is expected to be discontinued.

The environmental assessment had no significant findings.

The site inspections were considered adequate.

There are no outstanding chemistry issues.

For the tablets, an 18-month expiration is proposed for the blister packs and 24 months for the bottles.

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3 Biopharmaceutics

The clearance of valsartan in subjects with CHF is about 50% of that in normal subjects; this manifests as an increased AUC and C_{max}. The effect on clearance is difficult to reconcile with older data indicating that the principal means of elimination is through the feces as unchanged valsartan.

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4 Effectiveness

The sponsor submitted the results of 6 clinical studies in support of the indication in CHF. Three were studies of hemodynamics, two were studies of exercise tolerance, and one, Val-HeFT, was an outcome study.

4.1 Studies of hemodynamics

Study 102 was an open-label, study of acute hemodynamics in subjects with stable NYHA III-IV CHF. Three to 5 subjects per groups received single doses of placebo or valsartan, 10, 20, 40, 80, or 160 mg followed by assessments of PCWP and CO over 24 hours. This study showed little evidence of treatment-related effects on PCWP or CO.

Study 103 was a randomized, double-blind study of hemodynamics in subjects with stable NYHA II-IV CHF. Fifteen to 27 subjects per arm received twice-daily treatment for 2 weeks with placebo, lisinopril 10 mg, or valsartan 40, 80, or 160 mg. The primary end point was change from baseline in PCWP, measured at the inter-dosing interval. Nominally highly statistically significant reductions in PCWP were demonstrated for the 40 and 160-mg doses of valsartan. Marginal results were obtained with valsartan 80 mg and lisinopril. There was no apparent relationship between the dose of valsartan and the effect size. Other nominally significant effects of valsartan were an increase in cardiac index and reductions in systemic and pulmonary vascular resistance, but a relationship to dose was unclear.

The primary medical reviewer has questioned the ethics of Study 103, since it involved depriving subjects in placebo and valsartan arms of ACE inhibitor for 6 months prior to enrollment plus the 4 weeks of double-blind treatment. The 6-month period before enrollment is only an issue if one believes potential subjects gave up use of ACE inhibitors to have the opportunity to enroll; this seems unlikely. The 4 weeks of treatment is another matter. If ACE inhibitors are not in routine use where the study was conducted (Moscow), then it is likely that care extended during this study was superior to the prevailing local standard and, thus, to many of us, ethical.

Study 104 was a double-blind study of hemodynamics in subjects with NYHA II-IV CHF receiving background ACE inhibitor. Twenty-seven to 28 subjects per group were stratified by use of low- or high-dose ACE inhibitor and randomized to placebo or valsartan 80 or 160 mg b.i.d. for 4 weeks. There was no statistically significant effect of valsartan on the primary end point of PCWP at the inter-dosing interval.

4.2 Studies of exercise tolerance

Study 110 was a double-blind study of effects on 6-minute walk distance in subjects with NYHA II-III CHF. One hundred and forty-one subjects were randomized evenly to enalapril 10 mg b.i.d. or to valsartan 160 mg b.i.d., with final assessment at 12 weeks. This was a non-inferiority trial with predicted margin <45 m. Depending on how deaths and early withdrawals are handled, one gets slightly different nominal effect sizes, but the estimated treatment group difference was small—less than 10 m. Thus, the study was nominally successful.

Study 106 was a double-blind study of effects on treadmill exercise in subjects with NYHA II-IV CHF. One hundred eighty-five to 198 subjects per group were randomized to placebo or valsartan 40, 80, or 16 mg b.i.d., and followed for 16 weeks. Concomitant use of ACE inhibitors, but not beta-blockers, was permitted. Regardless of handling of subjects with no data at the final visit, there was no effect on either of two primary end points, treadmill exercise time or quality of life as assessed by the LHFQ questionnaire.

4.3 Study of clinical outcome

Study 107, Val-HeFT, was an international, double-blind study of 5010 subjects with NYHA II-IV CHF, possibly receiving background ACE inhibitor and beta-blocker,

randomized evenly to placebo or valsartan force-titrated over 4 weeks to 160 mg b.i.d. The two primary end points were time to all-cause mortality and time to a mortal-morbid event, assessed during 24-36 months of follow-up¹. Mortal-morbid events were any of all-cause mortality, resuscitated sudden death, hospitalization for CHF, need for intravenous inotrope or vasodilator for >4 hours. Morbid events were adjudicated by a committee blinded to treatment. Appropriate stopping rules were in place for mortality, and the trial was not stopped before 979 deaths had accumulated.

The effect on all-cause mortality was not statistically significant (valsartan : placebo hazard ratio of 1.02 with 95% confidence limits 0.90 to 1.15; p=0.8). The effect on mortal-morbid events was statistically significant (valsartan : placebo hazard ratio of 0.87 with 95% confidence limits 0.79 to 0.97; p=0.009²). The components of the mortality-morbidity end point are shown in Table 1.

Table 1. Components of mortality-morbidity end point (Val-HeFT).

	Placebo N=2499	Valsartan N=2511	Hazard	95% CI	P
All-cause mortality	484	495	1.02	0.90-1.15	0.80
CHF hospitalization	463	349	0.73	0.64-0.84	<0.0001
Resuscitation	30	20	0.66	0.38-1.17	0.15
CHF therapy	8	7	0.87	0.32-2.40	0.79

As shown, the major effect was a reduction in CHF hospitalizations. Total CHF- and cardiovascular-related hospitalizations similarly were reduced in the valsartan group.

The medical-statistical review investigated whether there were regional differences in effects on morbidity-mortality, and particularly if the US results, comprising about 45%, were different. The results do not appear to be materially different in the US.

The finding of an apparent effect on cause-specific hospitalization leads to the question of effects on all-cause hospitalization. The primary medical-statistical review reports prospective and retrospective analyses showing little effect on all-cause hospitalization, but the results suggest that the non-CHF and non-cardiovascular hospitalizations were similar in both groups.

Other prospectively defined secondary end points are summarized in Table 2.

Table 2. Other secondary end points (Val-HeFT)

	Favors	P		Favors	P
Cardiovascular mortality	Placebo	0.86	Signs & symptoms Paroxysmal nocturnal dyspnea Fatigue Edema Dyspnea at rest Dyspnea on effort Orthopnea Jugular venous distension Rales Third heart sound	Valsart	0.001
NYHA class	Valsart	0.001		Valsart	0.010
Ejection fraction	Valsart	0.001		Valsart	0.003
Left ventricular diastolic diameter	Valsart	0.0001		Valsart	0.037
				Valsart	0.003
Quality of life questionnaire	Valsart	0.004		Valsart	0.2
				Valsart	0.001
				Valsart	0.001
Overall	Valsart	0.004		Valsart	0.001
Physical	Valsart	0.009		Valsart	0.001
Emotional	Valsart	0.029	Valsart	0.22	

¹ The trial was to continue until 906 deaths occurred.

² The final alpha associated with each end point was 0.025.

Only the cardiovascular mortality end point leans, insignificantly, in favor of placebo. Symptomatic improvement is supported by effects on NYHA functional class, quality of life questionnaire, and various signs and symptoms.

The primary medical-statistical review also considered effects on morbidity-mortality by the following non-randomized factors: use of ACE inhibitor, use of beta-blocker (for which there was stratification), race, age, and gender. Effects by use of ACE inhibitor or beta-blocker are shown in Table 3. Effects by age, race, and sex are shown in Table 4.

Table 3. Mortality and morbidity-mortality by use of ACE inhibitors and beta-blockers (Val-HeFT) *

		Mortality			Morbidity-mortality		
		Beta-blocker			Beta-blocker		
		Yes	No	All	Yes	No	All
ACEI	Yes	n=226 109-1.85	n=672 0.81-1.11	n=898 0.93-1.21	n=381 0.97-1.45	n=1020 0.73-0.93	n=1401 0.82-1.03
	No	n=26 0.37-1.74	n=55 0.28-0.86	n=81 0.37-0.91	n=38 0.26-0.97	n=85 0.34-0.81	n=123 0.35-0.73
	All	n=252 1.05-1.73	n=727 0.79-1.06	n=979 0.90-1.15	n=419 0.91-1.33	n=1105 0.71-0.90	n=1524 0.79-0.97

*Cells show the number of events (not the number of subjects) and the 95% confidence limits for the valsartan:placebo hazard ratio.

Table 4. Mortality and morbidity-mortality by age, sex, and race (Val-HeFT)

		Mortality	Morbidity-mortality
Age	<65	n=402 0.94-1.24	n=678 0.76-1.02
	≥65	n=577 0.88-1.22	n=846 0.77-1.01
Sex	M	n=816 0.90-1.19	n=1131 0.80-1.00
	F	n=163 0.68-1.27	n=293 0.63-0.99
Race	Cauc	n=888 0.88-1.15	n=1350 0.78-0.97
	Black	n=60 0.89-2.52	n=120 0.84-1.74
	Other	n=31 0.36-1.46	n=54 0.26-0.77

Six hundred eighty-two subjects participated in a Val-HeFT sub-study of 6-minute walk exercise tolerance. Of these, 623 subjects had 6-minute walk test data at baseline and on treatment. The primary analysis did not distinguish valsartan from placebo (p=0.85), but it can be described as ruling out about a 3% treatment effect.

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5 Safety

The safety data reviewed in the primary medical-statistical review do not reveal issues related specifically to the use of valsartan in patients with CHF.

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6 Summary and recommendation

The Cardio-Renal Advisory Committee split 4-4 on whether valsartan should be approved for the treatment of heart failure. Their reticence had two components, concern about the overall strength of evidence and identification of the appropriate population to treat.

Several studies of hemodynamics failed to demonstrate effects of valsartan on pulmonary capillary wedge pressure, their primary end point. Several studies of exercise tolerance failed to demonstrate that valsartan affects exercise capacity. These studies may mean that valsartan does not affect wedge pressure or exercise capacity, but there are alternative explanations for these results. Nevertheless, Val-HeFT stands alone in support of the use of valsartan in heart failure.

The single-study strength of evidence argument starts with a nominal p-value of 0.009 for one of two primary end points for Val-HeFT. Since this was intended to be only one of two positive studies (there was hope that the second would be the exercise substudy of Val-HeFT), it was not really anticipated that this study would alone support the development program. Thus, Val-HeFT met its design goals, and the question is if that is good enough to support approval.

Val-HeFT's primary end points were mortality and combined morbidity-mortality. The study's power was prospectively divided by two for each end point, a very conservative approach, considering that the two end points are highly correlated; all subjects with a mortality event also contributed a morbidity-mortality event.

Furthermore, there is something special about mortality. The Agency (reasonably) acts as if all studies have "free" alpha to spend on mortality, regardless of whether or not it is declared an end point. From this perspective, the interpretation of $p=0.009$ should not be adjusted at all for multiplicity.

A variety of secondary end points support the positive findings on morbidity-mortality. Valsartan favorably affected CHF hospitalization, clearly the driving force behind the morbidity-mortality result, and it had favorable effects on NYHA class, ejection fraction, quality of life assessed by subjects, and most signs and symptoms of heart failure.

Does Val-HeFT meet the standard for support of a new indication by a single study? It depends on what one thinks the standard is or ought to be. The advice we often give sponsors is that two studies with $p<0.05$ are equivalent to a single study with $p<0.00125$, so this should be the target for a single study intended to support a new use. By this standard, even the most generous interpretation of Val-HeFT's p-value shows it falls short. But the Agency's regulatory behavior has not been predicated on a standard of $p<0.00125$. Table 5 shows, in ascending order of strength of evidence, specific indications awarded to ACE inhibitors and supported by a single study.

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Table 5. ACE inhibitors with indications based on single studies.

Drug	Trial	Indication	P-value
Enalapril	SOLVD-P	↓CHF hospitalization	0.001 ^a
Trandolapril	TRACE	↓mortality	0.042
		↓CHF hospitalization	0.047
Lisinopril	GISSI-3	↓mortality	0.04
Captopril	SAVE	↓CHF hospitalization	0.034
		↓mortality	0.02
	Diabetic nephropathy	↓progression	0.01
Ramipril	AIRE	↓mortality	0.002
		↓progression	0.017
		↓CHF hospitalization	0.011
	HOPE	↓myocardial infarction	0.0003
		↓stroke	0.0002
		↓cardiovascular mortality	0.0002

^aNot the primary end point.

Thus, even the most conservative interpretation of the Val-HeFT p-value, that it should be interpreted like 0.018, compares favorably with some prior approvals based on single studies.

If this trial can be considered adequate with regard to strength of evidence, then the issue is whether one knows in whom to use it. Resolution of that issue requires consideration of treacherous subgroup analyses. One fairly reasonable position is that one ought not consider subgroups at all; the best estimate the effect in a subgroup may be the effect in the overall population. The best feature of this position is that it is an unambiguous basis for decision-making.

As one steps away from the solid rock of subgroup agnosticism, one is clearly either hypothesis-generating or selecting the most likely interpretation; one's degree of certainty is not going to be as high as it is regarding analyses formally allocated alpha. What role does biological plausibility play in the interpretation of subgroup analyses? For Advisory Committee members Borer and Fleming, this was a crucial issue.

It is worth noting that Val-HeFT gives no reason to suspect that treatment effects are substantively different in the US compared with the rest of the world, in subjects under or over the age of 65, in males and females, or by race³. The weakest data exist with regard to race; only about 10% of subjects were non-Caucasian.

Subgroups in which there appear to be differences are those distinguished by use of ACE inhibitors and beta-blockers.

Despite there being relatively few subjects not on ACE inhibitors or not receiving beta-blockers and relatively few events in these subgroups, these subgroups account for much of the morbidity-mortality treatment effect. In addition, there appears to be a mortality reduction in the no-ACE inhibitor subgroup, and perhaps adverse mortality on beta-blockers. Because subjects were not randomized to use of ACE inhibitor or beta-blocker⁴, one needs to interpret these observations cautiously.

What is the plausible mechanism for such subgroup differences?

³ Clearly one cannot dismiss all subgroup analyses and still take comfort from those analyses that evidence no subgroup differences. If one is supposed to be concerned about effects by, e.g., age, sex, and race, must development programs allocate alpha to them? Is that more important than, e.g., getting dose-response data?

⁴ Although randomization was stratified for use of beta-blockers.

ACE inhibitors do not have class labeling for effectiveness, but it appears that specificity of indications among them has more to do with the technical problems of studying effectiveness for "hard" clinical end points for successive members of a class than it has to do with real differences among them. Angiotensin receptor antagonists and ACE inhibitors both block the renin-angiotensin system, so one's prior expectation is clear regarding likely additive effects.

The sponsor presented data at the Cardio-Renal Advisory Committee showing effects on blood pressure by subgroups of ACE inhibitor and beta-blocker use. One view of these data is shown in Table 6.

Table 6. Final on-treatment systolic pressure by treatment (Val-HeFT)

Drugs	ACEI	BB	Vals	SBP
0	No	No	No	123
1	Yes	No	No	120
	No	Yes	No	121
	No	No	Yes	119
2	Yes	Yes	No	120
	Yes	No	Yes	116
	No	Yes	Yes	119
3	Yes	Yes	Yes	116

Final systolic blood pressure tended to be lower the more drugs one was taking, including the addition of valsartan to ACE inhibitor, so there is an apparent additive effect for blood pressure, but it appears to be quite small.

Placebo group event rates were substantially higher in the subgroups not receiving ACE inhibitors or not receiving beta-blockers, as shown in Table 7.

Table 7. Placebo-group event rates (Val-HeFT)

		Mortality	Morbidity-mortality
ACE inhibitor	No	27%	43%
	Yes	19%	31%
Beta-blocker	No	23%	37%
	Yes	13%	23%

Perhaps subgroups not receiving ACE inhibitor or beta-blocker were sicker than subjects receiving them (placebo group mortality and morbidity-mortality event rates increase monotonically with NYHA class), but it is at least as plausible that subjects not receiving these drugs were simply under-treated for their heart failure.

What is known about effects on exercise tolerance can be summarized as follows:

Table 8. Exercise tolerance effects

	Treadmill	6-minute
Enalapril vs placebo	Improved ^a	No data
Valsartan vs placebo	Unaffected ^b	Unaffected ^c
Valsartan vs enalapril	No data	Similar ^d
^a Placebo-controlled study is basis for existing exercise claim in label for enalapril. ^b Study 106. ^c Sub-study of Study 107. ^d Study 110.		

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

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

INDICATIONS AND USAGE

Hypertension

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

Heart Failure

Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure for details.)

CONTRAINDICATIONS

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

WARNINGS

Fetal/Neonatal Morbidity and Mortality

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

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

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

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

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

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

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

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

Hypotension

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

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

Hypotension in Heart Failure Patients

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

PRECAUTIONS

General

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

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

Impaired Renal Function – Heart Failure: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.

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

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

Information for Patients

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

Drug Interactions

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

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

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

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (eg. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis.

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

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

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

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

ADVERSE REACTIONS

Hypertension

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

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

Diovan were headache and dizziness.

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

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

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

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

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

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

Body as a Whole: Allergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipation, dry mouth, dyspepsia, and flatulence

Musculoskeletal: Back pain, muscle cramps, and myalgia

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

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

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

Heart Failure

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

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

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

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

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

Post-Marketing Experience

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

Hypersensitivity: There are rare reports of angioedema;

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

Renal: Impaired renal function;

Clinical Laboratory Tests: Hyperkalemia;

Dermatologic: Alopecia.

Clinical Laboratory Test Findings

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

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

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

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

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

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

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

OVERDOSAGE

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

Valsartan is not removed from the plasma by hemodialysis.

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

DOSAGE AND ADMINISTRATION

Hypertension

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

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

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

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

Heart Failure

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Concomitant use with an ACE inhibitor and a beta blocker is not recommended.

HOW SUPPLIED

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

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

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

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

[See USP controlled room temperature.]

Protect from moisture.

Dispense in tight container (USP).

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Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

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CAPS NOV comments

Diovan®

valsartan

Capsules

Rx only

Prescribing Information

USE IN PREGNANCY

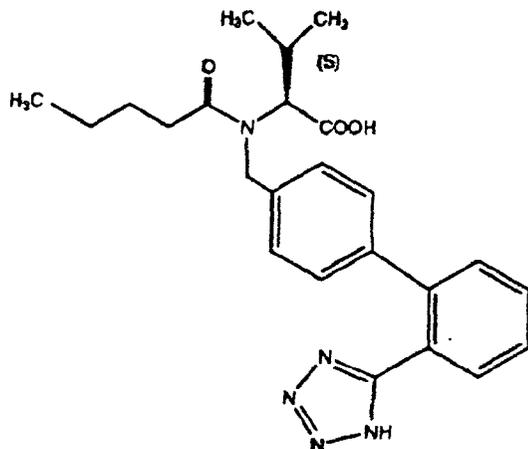
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.

See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

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

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



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

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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

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

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

Pharmacokinetics

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

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

Metabolism and Elimination

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

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution

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

Treadmill and 6-minute walk probably do not assess the same kind of exercise tolerance, so it is appropriate to consider them independently. Six-minute walk was unaffected by valsartan in one study, but it was similar to enalapril in another. Enalapril is not known to affect 6-minute walk, so the likely interpretation is that neither enalapril nor valsartan affect 6-minute walk. Treadmill exercise tolerance was improved by enalapril and unaffected by valsartan, in separate placebo-controlled studies. This suggests a real difference. However, Study 106, comparing valsartan with placebo for effects on treadmill exercise, was performed with most subjects receiving background ACE inhibitor. Thus, the available data do not exclude the possibility that valsartan could substitute for enalapril in prolonging treadmill exercise time.

Thus, shared mechanism of action for ACE inhibitors and angiotensin receptor antagonists leads to certain expectations regarding independent or additive effects on blood pressure, exercise tolerance, morbidity, and mortality, and these expectations are largely sustained by observations in this development program. The most likely outcome was that valsartan would add little when an ACE inhibitor was present, but that it would be capable of substituting for an ACE inhibitor.

Mechanistically, it is not so clear what interaction was to be expected of a beta-blocker and a renin-angiotensin system inhibitor. Angiotensin II receptors and beta-adrenergic receptors are coupled to adenylate cyclase, but, even where these receptors are co-located, an AT receptor antagonist can be expected to increase cAMP while a beta-blocker can be expected to decrease cAMP.

Practical experience in hypertension is largely lacking; among various antihypertensive combinations with ACE inhibitors, there are none approved or under development including a beta-blocker. However, there is experience in heart failure with background ACE inhibitor and beta-blockers carvedilol (CAPRICORN) and metoprolol (MERIT-HF). Informal analysis of CAPRICORN reveals no difference in carvedilol's effects on mortality rates in subgroups on and off background ACE inhibitor. Data from MERIT-HF are suggestive that risk reduction for mortal-morbid events was greatest in regions with the highest ACE inhibitor usage.

Thus, the experience with beta-blockers and ACE inhibitors in heart failure is consistent with independent benefits of each. Although this is not proven for beta-blockers and ACE inhibitors, it is likely to be true for them, and it is the most likely nature of the relationship between beta-blockers and valsartan. The increased mortality in the subgroup on beta-blockers is the weakest of the nominally significant subgroup findings, and it is the least likely to be reproducible.

In summary, sticking close to methodologically sound bases for decision-making, valsartan is clearly effective for reducing time to first mortal-morbid event in patients with heart failure. It does not meet a $p < 0.00125$ standard, but it is supported by prior expectations derived from experience with ACE inhibitors, and by Val-HeFT secondary findings pertaining to symptoms, cardiac function, and anatomy. It meets the standards the Agency uses to approve indications on the basis of single studies.

By its prospective analysis plan, Val-HeFT was successful in demonstrating that valsartan is effective in reducing the incidence of all-cause mortality plus CHF hospitalizations plus resuscitated sudden death plus need for intravenous inotropes or vasodilators, in a NYHA class II-IV population most of whom were receiving an ACE inhibitor and many of whom were receiving beta-blocker. In this study, valsartan appeared to have little effect on a second primary end point of all-cause mortality, effectively ruling out that valsartan is as much as 15% worse than placebo.

The label should show components of the primary end point and make the point that the primary effect is a reduction in hospitalizations for CHF. How much further to go in interpreting these data is a matter of judgement, but unplanned subgroup analyses

largely reinforce mechanism-based expectations, so this reviewer is strongly inclined to consider valsartan an alternative to ACE inhibitor and beta-blocker, with no implication for second-line use.

The sponsor's proposed label made more of the subgroup analyses, and, speaking for the sponsor at the Cardio-Renal Advisory Committee meeting, Dr. Jay Cohn said he believed the nominally significant increase in mortality in subjects receiving beta-blockers. However, the lack of plausible mechanism and the clean history of the use of beta blockers and ACE inhibitors argues that this is a spurious result.

There are no appropriate claims to be made from hemodynamic or neurohormonal data; what nominal findings there were came from studies failing on their primary end points. Perhaps the label should explicitly deny effects on pulmonary capillary wedge pressure.

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Norman Stockbridge
12/21/01 01:05:15 PM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review #2

NDA: 20-665/SE1-016
21-283/SE1-001

Sponsor: Novartis

Submission: In the Approvable letter of 24 October 2001, the sponsor was invited to submit a thorough analysis of findings pertaining to the population not on ACE inhibitor to support the hypothesis that valsartan was able to substitute for an ACE inhibitor. Retrospective analyses of these data are the subject of the sponsor's submission of 28 November 2001.

Review date: 10 December 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: The sponsor responds to the Approvable letter

Distribution: NDA 20-665

NDA 21-283

HFD-110/Project Manager

HFD-110/Stockbridge

Generally the baseline characteristics of the "ACE" and "no-ACE" groups were similar in Val-HeFT.

As previously noted, primary end point effects were larger in the group not on ACE inhibitors, as shown in Table 1.

Table 1. Primary end points (% , Val-HeFT)

	No ACEI				ACEI			
	Plac N=181	Val N=185	HR	P	Plac N=2318	Val N=2326	HR	P
Mortality	27	17	0.67	0.017	19	20	1.06	0.35
CV mortality	22	16	0.76	0.074	16	17	1.04	0.49
Morbidity	43	25	0.56	0.0002	31	29	0.90	0.10
Total non-fatal	27	13	0.46	0.0004	19	15	0.76	0.0003
CHF hosp	27	13	0.47	0.0006	18	14	0.76	0.0004

Thus, not only is the overall benefit in morbidity driven by the effects in the no-ACEI group, there is a likely mortality benefit manifest in the no-ACEI group, as well.

The sponsor's life table analyses show that effects on mortality and morbidity develop early and widen during the >2 years of follow-up.

Quality of life data (Minnesota Living with Heart Failure) were obtained in some countries. These data are consistent with a beneficial effect of valsartan in both ACEI and no-ACEI cohorts, but the magnitude of the treatment effect (valsartan minus placebo) is more than twice as large in the no-ACEI group. There was a similar trend of relatively improved quality of life score in the no-ACEI cohort of the exercise study 106.

LVEF and LVIDD data are consistent with beneficial effects of valsartan in both ACEI and no-ACEI cohorts, but the magnitude of the treatment effect (valsartan minus

placebo) is more than 3 times as large in the no-ACEI group. The reductions in norepinephrine and BNP levels were greater in the no-ACEI group.

The sponsor tabulated effects on various signs and symptoms of heart failure by the percentage of subjects who improved or worsened. As part of this review, the shift was assessed by the difference (percentage improved minus worsened) was calculated as a solitary indication of improvement, to compensate for any flattening of a distribution. Then the valsartan-minus-placebo difference was calculated as the overall treatment effect. Finally, the difference in treatment effect was taken between the no-ACEI and ACEI cohorts, to show if greater effects were seen in the no-ACEI cohort. The results are shown in Table 2.

Table 2. Effects on CHF signs and symptoms (Val-HeFT)

	Overall p-value	Effect favors	No-ACEI minus ACEI
Edema	0.003	Valsartan	15.0
Rales	0.001	Valsartan	11.8
Jugular venous distension	<0.001	Valsartan	5.4
Paroxysmal nocturnal dyspnea	0.001	Valsartan	4.9
Dyspnea at rest	0.029	Placebo	3.5
Orthopnea	0.11	Valsartan	-0.5
NYHA class	<0.001	Valsartan	-2.2
Fatigue	0.008	Valsartan	-3.6
Dyspnea on exertion	0.001	Valsartan	-4.5
Third heart sound	0.2	Valsartan	-4.8

Edema, rales, JVD, and PND all had robust effects overall, but larger effects in the no-ACEI cohort. There were overall effects on NYHA class, fatigue, and dyspnea on exertion, but somewhat larger effects in the ACEI cohort. Thus, there is no consistency with respect to CHF signs and symptoms by concomitant use of ACE inhibitors.

Six minute walk was assessed in about 25% of subjects in Val-HeFT. Overall, there was no net effect ($p=0.85$), but there was a nominally significant ($p=0.02$) effect in the no-ACEI cohort of 35 subjects¹.

Treadmill exercise was evaluated in Study 106; there was no overall treatment effect ($p=0.2-0.85$ for various dose groups vs. placebo). In the cohort not receiving ACEI (about 14%), the effects were generally not nominally statistically significant, but the effects did favor active treatment and the estimated effect sizes were larger than in the cohort receiving ACEI.

The sponsor's response to the approvable letter answers the question posed as well as available data can. The results for Val-HeFT and the exercise tolerance study (106) are largely consistent with the hypothesis that valsartan can substitute for an ACE inhibitor in producing the ACE inhibitor's expected benefits in heart failure. These benefits include effects on mortality (chiefly cardiovascular), morbidity (chiefly heart failure hospitalizations), exercise tolerance (probably), ejection fraction, heart size, norepinephrine and BNP levels, and, perhaps, some of the signs and symptoms of heart failure.

¹ The sponsor's analyses assigned 0 distance to subjects who died or were unable to walk because of heart failure.

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Norman Stockbridge
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MEDICAL OFFICER

**Medical-Statistical Review:
NDA 20-665/SE1-016 and 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets**

September 13, 2001

**Primary Medical Reviewers: Shari L. Targum, MD, Medical Officer, Division of Cardio-Renal Drug Products, HFD-110, ODE1/CDER.
(Study 110 was reviewed by: Abraham Karkowky, MD, PhD, Team Leader, Division of Cardio-Renal Drug Products, HFD-110, ODE1/CDER.)**

Statistical Reviewer: Study 107 was reviewed by: H.M. James Hung, PhD, Statistician/Team Leader, Division of Biostatistics, HFD-710, CDER.

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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) 23

Study 103. A multicenter, double-blind, randomized, placebo- and active-controlled, between patient trial to assess the cardiac hemodynamic effects of valsartan 40 mg, 80 mg and 160 mg, all twice daily, in patients with chronic stable congestive heart failure NYHA stage II-IV treated for four weeks (Phase II) (Protocol date: January 25, 1995) 40

Study 104: A Double-Blind, Placebo-Controlled, Dose Response Trial to Determine the Acute and Chronic Central Hemodynamic Effects of Valsartan in Patients with Symptomatic Congestive Heart Failure. (Phase II) (Dec. 5, 1994) 56

Study 106: Multicenter, randomized, double-blind, placebo-controlled, parallel trial to assess the effect of valsartan on exercise capacity, quality of life, and signs and symptoms, in patients with stable, chronic, congestive heart failure (NYHA Class II-IV) (Phase III) (Protocol date: 12-16-96) 67

Study 107: Multicountry, randomized, double-blind, parallel, placebo-controlled trial to assess the effect of valsartan on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV) (Phase III) 83

Study 107 (Substudy 02): Multi-country, randomized, double-blind, placebo controlled trial to assess the effect of valsartan on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV): Six-Minute Walk Substudy. (Phase III) (Protocol date: June 9, 1997) 108

Study 110. A twelve week, multicenter, randomized, double-blind, active-controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity in patients with stable, moderate, chronic heart failure 114

Recommendation on Approvability

Medical Reviewer's Comments:

As seen in the Val-heft study (107), no survival benefit has been demonstrated with valsartan. However, benefit was seen with valsartan with respect to prolonging the time to first morbid event, as driven by CHF hospitalization. Subgroup analysis shows greater valsartan benefit (mortality and morbidity) in the subgroups not on background ACE inhibitor or beta blocker, versus those patients on background ACE inhibitors/beta blockers (albeit with small numbers of patients not on background ACE inhibitors). The results were less favorable in the US population compared to the non-US population. Some secondary endpoints (LHFQ, EF, signs/symptoms, neurohormone measurements) have been favorable for valsartan (consistently only in Study 107). Interestingly, the increase in EF and neurohormones in this study population were not accompanied by a survival benefit. No benefit has been demonstrated for valsartan in prolonging the time to all-cause hospitalization, and the Days Alive/Out of hospital analysis did not show a substantial difference in favor of valsartan.

Outstanding questions and requests for the sponsor include: 1. Primary reason for non-CHF hospitalization; 2. Further analysis of renal safety, including numbers of patients dialyzed; 3. SAS code for first hospitalization; 4. Case report forms for angioedema.

The medical reviewer concludes that valsartan appears to have some beneficial effect in terms of CHF hospitalization. A remaining issue is whether this benefit is "offset" by safety issues related to this drug, and whether drug-related side effects contribute to the lack of significant benefit seen in "all-cause" hospitalization. The Agency, at the time of this review, is still awaiting further data/analysis from the sponsor regarding this issue.

If convincing information can be presented to alleviate this concern, then the Medical Reviewer would recommend that valsartan is approvable in prolonging the time to first morbid event in this particular patient population. (The reviewer wonders if the outcome would have been different if, for example, there had been a higher usage of beta blockers in this patient population).

Recommendation on Phase 4 Studies and/or Risk Management Steps

Further studies of Valsartan in CHF could include:

- The role of valsartan in treatment of CHF in those patients who are intolerant to ACE inhibitors. Ideally, this type of trial would be placebo-controlled, evaluating morbid/mortal outcomes. Since the numbers of Black patients was relatively small compared to the total, this reviewer would be interested in:
 - The efficacy and safety of valsartan in CHF therapy in the Black population.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Valsartan (Diovan) is an orally active competitive angiotensin II antagonist approved for the treatment of hypertension. The recommended starting dose is 80 mg once daily in patients who are not volume-depleted. Valsartan may be used over a dose range of 80 to 320 mg once daily. No initial dosage adjustment is required for the elderly or those with mild to moderate hepatic or renal insufficiency. Safety and efficacy in pediatric patients has not been established.

The Sponsor has submitted an efficacy supplement for the treatment of CHF. The proposed regimen is a starting dose of 40 mg twice daily, with up-titration to 80 mg and 160 mg twice daily 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 160 mg twice daily.

B. State of Armamentarium for Indication(s)

There are currently no angiotensin-II antagonists approved for the treatment of CHF.

Current therapy for CHF includes the use of: diuretics, digitalis, ACE inhibitors, beta blockers (such as carvedilol and metoprolol (symptomatic Class II and III CHF)).

C. Important Milestones in Product Development

1. In a July 7, 1994 telephone conference with the Agency, the Vheft-IV study, a 3-4 year, randomized, double-blind, placebo-controlled, forced titration study in about 600-1,000 NYHA Class II-IV patients, was discussed. This was planned as one trial in patients on a background of ACE inhibitors, diuretics and digoxin and another trial in patients who are intolerant to ACE inhibitors, on a background of digoxin and diuretics. The arm with ACE inhibitor-intolerant patients was planned with exercise tolerance as an endpoint, since it was felt that the sample size would be insufficient for a mortality endpoint. The Agency responded that unless the results were quite significant for a survival benefit (i.e., p of less than 0.0025), the Agency would have to "think a long time" about what to do with the supplement. The Agency encouraged the sponsor to conduct dose-ranging morbidity/mortality trials. In addition, the Agency expressed discomfort if Vheft-IV were the only source of data, but would likely accept Vheft-IV plus two or more ETT trials; however, the Agency needed to know the trial designs in greater detail.
2. In an April 5, 1996 End-of-Phase II meeting, it was noted that choosing an appropriate endpoint in CHF trials was difficult. For a combined endpoint, there may be approvability issues if all parts of the combined endpoint do not have results in the same direction. Furthermore, approval based on one trial would need robust results, dose-related effects, or other reasons to believe that results were reproducible. The sponsor agreed to revise the stopping rule for Study 107 (to be based on mortality alone). The sponsor also considered having two primary endpoints, all-cause mortality and the combined endpoint (for 107). The sponsor planned to send a sealed copy of the randomization codes to their IND, and provide pharmacokinetic data from CHF patients given BID dosing.

D. Other Relevant Information

Valsartan is currently marketed in many countries for the indication of hypertension. At the time of the submission, an application was being made to the German health authority for the treatment of heart failure.

E. Important Issues with Pharmacologically Related Agents

Since approval of angiotensin-II antagonists (sartans) for the treatment of hypertension, there have been reports of elevated liver function tests. In addition, there have been rare reports of angioedema and anaphylactic reactions.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

According to the assigned chemist, a pending issue in this submission involves expiration dates for this drug. For further detailed information, please see the review by the assigned chemist. An abbreviated preclinical pharmacology summary was submitted (Volume 1). There was evidence, based on animal models, that valsartan reduced preload (dog model) and reduced systemic and pulmonary vascular resistance without affecting arterial blood pressure (pig model). In another dog study, long-term valsartan therapy decreased preload and afterload in moderate heart failure but provided only limited benefit in attenuating progression of LV dysfunction. Some favorable outcomes were noted regarding remodeling. No animal pharmacology/toxicology issues have been identified with this submission.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics/Pharmacodynamics

The pharmacokinetics of valsartan in CHF patients are similar to those of healthy volunteers with respect to linearity, T_{max} (about 3 hours), T_{1/2} (about 6.5 hours) and age effects. Valsartan clearance was about 10-20% lower in the elderly CHF patients compared to younger CHF patients.

The clearance of valsartan appears to be reduced about 50% in patients with CHF compared to healthy subjects. C_{max} and AUC are ~1.3 to 2 times higher in patients with CHF compared to healthy subjects. Accumulation of valsartan is slightly greater in patients with CHF when dosed at 40-160 mg BID compared to once daily in hypertensives.

For further detailed discussion, please see the Clinical Pharmacology and Biopharmaceutics Review.

IV. Description of Clinical Data and Sources

A. Overall Data

The source of data used in the review consisted of the clinical trials conducted by the sponsor (see Table 1). In addition, there was an uncontrolled study (ANG 102) report in the efficacy supplement which was unaccompanied by a database.

In addition, literature reports, current labeling and postmarketing data were used as needed.

Integrated Summary of Efficacy:

The five double-blind studies are summarized in Table 1 (below).

Table 1. Double-blind Studies

Study	Control	Treatment duration	No. randomized	CHF Class	Entry criteria	Treatment	Efficacy
103	Placebo/active	4 weeks	116	II-IV	PCWP \geq 15 mmHg (-ACE)	V40 bid, V 80 bid, V 160 bid, PBO, Lis 5/10 qd	Hemodynamics and neurohormones
104	Placebo	4 weeks	83	II-IV	LVEF \leq 40%, PCWP >15 mmHg (+ACE)	V 80 bid, V 160 bid, PBO	Hemodynamics and neurohormones
106	Placebo	16 weeks	770	II-IV	LVEF \leq 40% (+/-ACE)	V 40 bid, V 80 bid, V 160 bid, PBO	ETT, LHFQ, signs/symptoms, NYHA, EF
107	Placebo	24-36 months	5010	II-IV	LVEF < 40, LVIDD>2.9mm /m ² , (+/-ACE)	V 40-160 bid forced titration, PBO	Morbid/mortal, 6 min. walk substudy, signs/symptoms, NYHA, LHFQ, EF, LVIDD, neurohormones
110	Active	12 weeks	141	II-III	LVEF \leq 45% +prior ACE	V 80-160 bid, Enal 5/10 bid, titration	6 min. walk, signs/symptoms, NYHA, LHFQ, AVPD, LVIDD

Study 102. This was a 3-site open-label, placebo-controlled, single-dose study of the effects of valsartan 10, 20, 40, 80 and 160 mg and placebo on central hemodynamic and neurohormone measurements in patients with Class III-IV stable CHF. Three to five patients were randomized per treatment group. The primary efficacy parameter was the change from baseline in PCWP and CO at 1, 2, 3, 4, 6, 8 and 12 hours after dosing. Baseline imbalances were seen between placebo and treatment groups (PCWP higher in placebo and showed largest decreases). No dose-response pattern could be seen in reviewing the hemodynamic data. Valsartan exhibited linear kinetics consistent with that seen in healthy volunteers. There was a trend toward increase in placebo-adjusted mean change for PRA and Ang II and a decrease in aldosterone concentrations with increasing valsartan concentrations.

Study 103. This was a 9-site double-blind, randomized, placebo and active-controlled study of the effects of valsartan 40, 80, and 160 BID, placebo, and lisinopril 5 titrated to 10 mg QD on central hemodynamic and neurohormone measurements in patients with stable Class III-IV CHF. Patients were allowed in this trial if they were not taking ACE inhibitors for 6 months prior to Visit 1. The primary efficacy variable was the change from baseline in PCWP. Twenty-four to 27 patients were randomized to valsartan or placebo, and 15 patients were randomized to lisinopril. At Day 28, valsartan 40 BID and 160 BID showed a statistically significant decrease in PCWP compared to placebo; the results for valsartan 80 BID were inconsistent and showed a nonsignificant trend at 12 hours post-dosing. Study 103 will not be used by the medical reviewer for decision-making; please see the detailed study review for further details.

Study 104. This was a multicenter, double-blind, randomized, placebo-controlled 4 week study of Class II-IV CHF patients on background ACE therapy. Eighty-three patients were randomized to either valsartan 80 BID, valsartan 160 Bid or placebo. The primary efficacy parameter was the change from baseline in PCWP. Other measures included other hemodynamic parameters and neurohormones.

Study 106. This was a multicenter, double-blind, randomized, placebo-controlled study evaluating effects of valsartan 40 BID, 80 BID, 160 BID or placebo on exercise time and the LHFQ. Seven hundred seventy patients were randomized. The primary efficacy parameters were change in mean exercise tolerance time (ETT) via modified Naughton protocol as well as the overall LHFQ. Secondary measures included signs/symptoms of CHF and EF. Patients were stratified according to ACE inhibitor use (y/n).

Study 107. This was a multinational, double-blind, forced titration, placebo-controlled study of 5010 Class II-IV CHF patients. The study was event-driven, ending after a prespecified number of deaths. Patients were randomized to valsartan 40 BID or placebo with forced titration to a maximum dose of 160 BID. The primary efficacy parameters were: time to death and time to first morbid event (composite). Secondary variables included: time to first nonfatal morbid event, time to CHF hospitalization, time to CV death, NYHA class, signs/symptoms of CHF, change in EF, change in LVIDD, change in overall, physical and emotion LHFQ. Patients were stratified according to beta blocker use (y/n).

Study 110. This was a randomized, double-blind, active controlled 12 week study of Class II-III CHF patients on background ACE inhibitor. One hundred forty-one patients were randomized to valsartan (80 to 160 mg once daily) or enalapril (5 to 10 BID). The primary efficacy parameter was the six minute walk test.

Morbidity and mortality results:

One study, 107, evaluated the effect of valsartan on mortality and morbidity. To avoid redundancy in data presentation, the reader is referred to the Individual Study Review, where the efficacy tables are presented and the study is discussed in detail. It can be seen (Efficacy tables, Study 107) that there is no survival benefit for valsartan in this study population. However, valsartan did significantly prolong the time to first morbid event. This co-primary endpoint appears to be driven by CHF hospitalizations. Indeed, valsartan also significantly prolonged the time to first CHF hospitalization. This finding is consistent whether assessed by the Investigator or the Endpoint Adjudication Committee.

The most common cause of death in the 107 study population was sudden cardiac death. Subgroup analysis for mortality and morbidity results did not show meaningful differences in age and gender. Analysis of the mortality subgroups showed statistically significant findings only in

the group not on ACE inhibitor and the group taking beta blocker. The "no ACE" group showed a hazard ratio of 0.669 in favor of valsartan; the group on beta blocker showed as hazard ratio of 1.357 against valsartan.

Morbidity subgroups showed similar hazard ratios except that valsartan appeared to show less benefit in the US, in patients with ischemic CHF, in the subgroup with higher EF, and in Black patients (although the number of Black patients was small relative to the total). Valsartan appeared to show less benefit in the subgroup on background ACE inhibitor; the results of morbid events for patients on beta blocker appeared to be unfavorable in the valsartan group. Further analyses of CHF hospitalization can be found in the Study Review of 107.

Exercise testing results:

Studies 106, 110 and 107 (substudy 02) utilized various exercise testing. Study 106 used a modified Naughton protocol. Studies 107 (02) and 110 used the 6 minute walk. In all three studies there was an improvement in exercise capacity compared to baseline; this included an improvement in the placebo group. No statistically significant improvement in valsartan was seen compared to placebo. The results do not support a claim for improvement in exercise capacity for valsartan compared to placebo.

Ejection fraction results:

In both Studies 106 and 107, significant increases in LV EF were seen with valsartan compared to placebo. In study 106, significant increases were seen at endpoint for valsartan 40 mg BID and 160 mg BID (the results for 80 BID showed a nonsignificant trend).

LHFQ:

The Minnesota Living with Heart Failure Questionnaire (LHFQ) was measured in Studies 106, 107, and 110.

Only Study 107 showed statistically significant results in overall LHFQ. Subgroup analysis of the LHFQ endpoint results (107) show improvement in the "no ACE" subgroup compared to placebo (worsening). A review of the 107 emotional and physical scores also show significant improvements in the valsartan group.

Central hemodynamic measurements:

Studies 102, 103 and 104 used right heart catheterization to measure central pressures. In all three studies the primary efficacy variable involved change in PCWP. Study 104 showed a statistically significant decrease in PCWP at peak (4-8 hours post dosing) and over 0-12 hours for valsartan 160 mg BID, the highest dose used, as measured on Day 0 (first dose). However, a statistically significant difference compared to placebo was not seen on Day 28. Statistically significant differences were seen in the decrease in PCWP compared to placebo for valsartan 160 mg BID in Study 103 (where patients were off ACE inhibitors). Because of baseline differences across treatment groups in Studies 102 and 104, the medical reviewer is cautious in the interpretation of these results.

Dyspnea-fatigue Index:

This result, from study 110, showed a slight improvement in symptoms with no statistically significant differences.

LVIDD:

Significant decreases in LVIDD/BSA were seen in valsartan vs. placebo (107).

Neurohormone results: