

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-665/S-016

NDA 21-283/S-001

Administrative Documents

Time Sensitive Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA 20-665

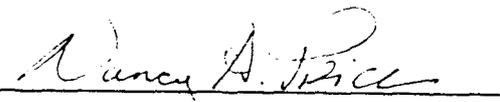
The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Diovan®
Active Ingredient: Valsartan
Strengths: 40 mg, 80 mg, 160 mg, 320 mg
Dosage Form: Tablets

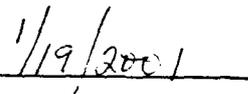
U.S. Patent Number: U.S. 5,399,578
Expiration Date: March 21, 2012
Type of Patent: Drug Substance, Drug Product and Method of Use
Name of Patent Owner: Novartis Pharmaceuticals Corporation

The undersigned declares that the above U.S. Patent number 5,399,578 covers the composition, formulation and/or method of use of Diovan® (valsartan). This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act for the treatment of hypertension and is the subject of this application for the treatment of heart failure, for which approval is being sought.

Signed



Date



Nancy A. Price
Associate Director
Drug Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 20-665
#21-283

SUPPL # SE1-016 (capsules)
SUPPL# SE1-001 (tablets)

Trade Name: Diovan Generic Name: Valsartan

Applicant Name: Novartis Pharmaceuticals Co. HFD # 110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) _SE1_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / X /

If yes, NDA # Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-665 Diovan (valsartan) Capsules

NDA# 21-283 Diovan (valsartan) Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 106 and 107

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 106 and 107 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / / NO / / Explain: _____

Investigation #2

IND # YES / / NO / / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/
NO /_X_/

If yes, explain: _____

/S/

Signature Date
Title:

/S/

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Raymond Lipicky
10/16/01 04:08:20 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-655 & 21-283 Supplement Type (e.g. SE5): SE1 Supplement Number: S-016 & S-001

Stamp Date: April 27, 2001 (20-665/S-016) & July 23, 2002 (21-283/S-001) Action Date: 9/30/02

HFD 110 Trade and generic names/dosage form: Diovan (valsartan) Tablets and Capsules

Applicant: Novartis Pharmaceuticals Therapeutic Class: Angiotensin II Antagonist

Indication(s) previously approved: Hypertension

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study

- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min X kg _____ mo. _____ yr. <1 month Tanner Stage _____
 Max X kg _____ mo. _____ yr. <17 years Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 9/30/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

NDA #-###

Page 3

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

APPEARS THIS WAY
ON ORIGINAL

8/8/01

TO: NDAs 20665 and 21283

FROM: Stephen Fredd, M.D., HFD-110.

SUBJECT: Requested Waiver of Pediatric Studies

On April 27, 2001 Novartis submitted a supplemental application for the use of Valsartan in adults with CHF. In response to our May 18, 2001 letter which raised the issue of pediatric studies, the company has requested a full waiver of such studies.

21CFR314.55 contains the regulations re the pediatric rule. A draft guidance has been available to assist industry in addressing the rule. Briefly the regulation requires sponsors to provide data adequate to assess the safety and effectiveness in the pediatric population of a drug product submitted for approval in adults for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. The regulations provide for a deferral of the requirement if the drug is ready for approval in adults, or a full waiver. A waiver may be granted if: the drug does not appear to provide a meaningful therapeutic advance for pediatric patients and is not likely to be used in a substantial number of children; studies are impractical or impossible to conduct because the number of patients is so small or the patients are too geographically dispersed; or evidence suggests that the drug would be ineffective or unsafe. Partial waivers are also possible for particular pediatric age groups. The regulations give a definition of meaningful therapeutic benefit; i.e. if FDA estimates that if approved the drug would represent a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products adequately labeled for that use.

The draft guidance restates much of what is in the regulations and for a full waiver provides an attachment that might be used to request a waiver. Utilizing this attachment, Novartis has requested a waiver based on the impracticality of doing such studies because of the small number of pediatric patients with CHF.

To support their request, Novartis used the National Hospital Discharge Survey for 1997 and 1998. Heart failure was the primary discharge diagnosis for 2,899 patients in 1997 and 4,947 in 1998, ages 1-19 years. Citing that the agency has given a 50,000 number as the cut-off for the determination whether there are a substantial number of pediatric patients, they claim that they have met the waiver requirement. They further state that they intend to perform pediatric studies of Valsartan for hypertension.

Comments:

The sponsor has requested a waiver based on the impracticality of doing pediatric studies in CHF because of the small number of pediatric patients with CHF. The number given is based on the incidence of pediatric CHF hospital discharges and does not include those children with CHF who do not require hospitalization. Even if we agreed that the number of available patients for study is around 5000 yearly, the sponsor makes no case that useful studies in pediatric patients are impossible or impractical. It seems inherent in this particular basis for waiver that the sponsor provide draft pediatric studies to the agency with their evaluation of the practicality of performing these studies.

The waiver criterion invoked by the sponsor depends on the size of the patient population as does the criterion that requires both a small patient population and a determination that the product would not represent a meaningful therapeutic advance for the pediatric population. The "impractical" criterion should not be used to avoid the "advance" criterion.

We have issued a written request for pediatric studies of Milrinone, and we have ACE inhibitors on the list of drugs that should be studied for CHF in pediatric patients. If Valsartan were approved for the treatment of CHF in adults, there would be some presumption that it would be safe and effective in children. Other drugs submitted for treatment of CHF in adults might also be useful in children with CHF. Were we to grant a waiver to Novartis on the basis that studies of CHF in children are impractical or impossible, that determination could affect many other drugs that could be beneficial to children with CHF including ACE inhibitors that are on our list of drugs that should be studied.

While a request for deferral of pediatric studies could be considered if Valsartan was ready for approval in adults, I would recommend that, on the basis of what the sponsor has provided, a full waiver of pediatric studies not be granted.

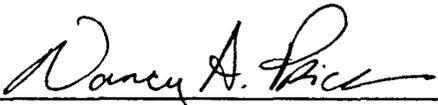
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stephan Fredd
8/8/01 07:56:32 AM
MEDICAL OFFICER

DEBARMENT CERTIFICATION

NOVARTIS PHARMACEUTICALS CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act, in connection with this application.

Signed 

Date 6/13/2001

Nancy A. Price
Associate Director
Drug Regulatory Affairs

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 23, 2002

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Approval of Valsartan for heart failure in patients intolerant of ACEI's

TO: File NDA 20-665/SE1-016; 21-283/SE1-001

I. Introduction

ValHeFT was a large randomized trial comparing Valsartan 40-160 mg b.i.d. and placebo in patients with symptomatic CHF and an EF < 40%, LV internal diameter in diastole > 2.9 cm/m² (i.e., systolic dysfunction). The co-primary endpoints of the trial were all cause mortality and "morbidity" [all cause mortality plus morbid events (sudden death resuscitated, hospitalization for CHF, or I.V. inotrope or vasodilator for ≥ 4 hours without hospitalization)]. Its aim was primarily to examine the effect of an angiotensin II antagonist (AIIb) in a population of patients already receiving an ACEI (for theoretical reasons not important here it was thought an AIIb might have effects additive with ACEI's). The trial design was "simple" or "real world," so that background therapy was unspecified and left to the investigator. As a result (fortunately) some patients were not on an ACEI at all and those who were on an ACEI often were on less than the recommended dose. The study thus tests two different hypotheses, although it was not designed to do so: (1) the benefit of an AIIb added to ACEI treatment and (2) the usefulness of an AIIb alone in addition to background therapy not including an ACEI. With respect to (2) the vast experience with ACEI's in evaluating the effectiveness of a treatment that decreases the amount of angiotensin II would seem pertinent to a treatment that blocks the effect of angiotensin II (on blood vessels, at least); i.e., the ACEI data represent something of "a prior."

The ValHeFT gave the following overall results.

	Events		HR	p-value
	Valsartan n=2511	Placebo n=2499		
All-cause mortality	495 (19.7%)	484 (19.4%)	1.02 (0.90-1.15)	0.80
Morbidity	723 (28.8%)	801 (32.1%)	0.87 (0.79-0.97)	0.009

As can be seen in the table, the favorable results is driven entirely by a reduction in non-fatal morbidity, primarily heart failure hospitalization.

The overall result on one of the 2 primary endpoints is moderately strong, even if compared to a critical alpha of 0.025 (2 endpoints) but, as explained below, I do not believe a recommendation for use of valsartan in all patients, including those on an ACEI, is supported by the study (even though 93% of patients in ValHeFT were receiving one) and that labeling valsartan for that use would be an error. To avoid that error we must look at a critical subset of the study, the 7% of patients not receiving an ACEI, in whom the effect of valsartan is much larger than in the 93% of patients receiving an ACEI.

I am well aware of the dangers of subset-looking and have my own slides showing Peto's zodiacal sign analysis of ISIS II. Nonetheless, if the overall study shows a significant effect at an acceptable level of statistical significance it seems reasonable to inquire into where the effect is coming from, particularly when there is a very strong pharmacologic rationale for distinguishing between people on, and people not on, an ACEI. Indeed, if we cannot look at the subset and must consider only the overall study, then we presumably must approve valsartan for use with or without an ACEI. This would be a significant error in my view, partly because there is little evidence of benefit in people on ACEI's and partly because there is a suggestion of an adverse interaction of valsartan added to an ACEI plus a beta blocker. This adverse interaction may or may not be real, but in the absence of any reason to add valsartan to an ACEI, there seems to reason to accept this potential risk. Note that there is no suggestion that valsartan alone (no ACEI) has an adverse interaction with a beta blocker.

II. Results on Primary Endpoints and Major Secondary Endpoint in the No-ACEI and ACEI Subsets

If ValHeFT is broken into ACEI and no-ACE subgroups, the following results are seen.

(from Dr. Stockbridge's 6 Feb 2002 Review)

	Primary endpoints (%)							
	No ACEI				ACEI			
	Placebo n=181	Val n=185	HR	P	Placebo n=2318	Val n=2326	HR	P
Mortality	27	17	0.67	0.017	19	20	1.06	0.35
CV Mort	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	0.46	0.0006	18	14	0.76	0.0004

Mortality plainly leans adverse in the large ACEI-taking group, but morbidity (which as defined includes mortality) leans favorably, largely because of an effect on CHF hospitalization. Even this residual benefit, however, is strongly affected by the ACEI dose. If results are shown by ACEI dose (below vs. at or above recommended dose), it is clear that much of the residual effect is driven by patients not receiving at least the recommended dose of ACEI.

(from Dr. Stockbridge's 6 Feb 2002 Review)				
Use of ACEI's - RR (V/P160)				
	None	Low	Any	High
	n=366	n=2035	n=47644	n=2572
mortality	0.67	0.99	1.06	1.15
morbidity	0.56	0.86	0.90	0.96
CV mortality	0.76	0.95	1.04	1.17
non-fatal morbidity	0.46	0.73	0.76	0.79
CHF hosp'n	0.47	0.71	0.76	0.81
non HF hosp'n	1.02	1.11	1.03	0.93

Thus what little effect valsartan has in people on ACEI's (HR 0.9 for overall morbidity and the larger effect on CHF hospitalization) is considerably reduced in patients on adequate doses of ACEI. Some effect may remain in people on ACEI's, but even this could be the result of less than full compliance with the non-study medications.

My conclusion is that there is a favorable overall result on morbidity in ValHeFT, but that this effect is driven largely, perhaps entirely, by the no-ACEI group, and that the effect in the subgroup is large and very highly statistically significant despite the small size of the subgroup. Given the overall favorable effect in ValHeFT, at a reasonable level of statistical significance (i.e., a positive study), the absence of an effect in the large ACEI group (therefore no basis for use in that group), we can conclude that valsartan has an effect on morbidity in patients not receiving an ACEI.

A mortality effect is also suggested in the no ACEI subgroup, but, as Dr. Hung points out, the p-value is not extreme ($p=0.017$) there is no overall effect on mortality to "allow" pursuit of subgroups; also, and this was clearly not a planned subset (that is also true for morbidity but there the extreme p-values make a difference). Dr. Hung argues strongly that a mortality effect has not been demonstrated, and should not appear in labeling and I agree, although there is certainly a suggestion of one.

III. Supportive Data

The above reasoning, I believe, supports approval of valsartan for use in patients not receiving ACEI's. Apart from the modest total experience with AIIB's compared to ACEI's, another reason to limit claims to that group is the finding of an adverse effect on mortality and morbidity in the subgroup of people on ACEI's and beta blockers (HR about 1.4 and 1.2, respectively). Whether this is real or not, if valsartan is not used in people receiving ACEI's the issue does not arise.

ValHeFT evaluated symptoms, exercise ability (in a subgroup) and QOL (Minnesota Living with Heart Failure) in some countries. For symptoms, almost all of which were favorably effected overall, the effect was numerically larger in the no ACEI subgroup for rales, edema, jugular venous distension, PND, and dyspnea at rest, but numerically worse in the no-ACEI subgroup for orthopnea, NYHA class, fatigue and DOE.

Six-minute walk was assessed in 25% of patients, with no overall effect shown ($p=0.85$). In the no-ACEI subset, however, there was a nominally significant effect ($p=0.02$) in a group of just 35 subjects, with an 84 m increase on valsartan compared to no treatment (50 m improvement on valsartan and 34 m deterioration on placebo). A similar trend was seen in study 106 comparing valsartan 80, 160, and 320 mg

vs. placebo. There were about 180 patients per group overall, with about 20-25 receiving no ACEI. The treatment effects (placebo-subtracted) overall were 3-20 m (all very NS) but were 120, 50 and 66 m in the 80, 160 and 320 mg subgroups. Only the low dose showed statistical significance but the results overall are very similar to the ValHeFT exercise substudy.

IV. Conclusions

Valsartan should be approved for use in patients with low EF congestive heart failure who cannot tolerate an ACEI. The evidence for effectiveness with respect to outcome arises from a single 5000 patient study comparing valsartan and placebo, each added to baseline therapy, which usually (93%) included an ACEI. With respect to morbidity, the study favored valsartan, with a fairly small p-value ($p=0.009$) but most of this effect arises from a 360 patient subset of the larger study – patients not on ACEI's. The effect on morbidity (principally death plus hospitalization for CHF) was large (a 44% reduction) and highly significant ($p=0.0002$). The subset, while not a planned secondary endpoint, was pharmacologically sensible and, as noted, accounted for almost all of the overall effect seen in ValHeFT.

The limitation to people intolerant of ACEI's is a close question. The use of the drug in no-ACEI subset is strongly supported, but principally by a subset analysis of a larger trial (which, it must be acknowledged, also showed a favorable overall effect). There is some further support for an effect in the no-ACEI subgroup on 6 minute walk distance, further strengthening the case. On the other hand, use of ACEI's in CHF is supported by a large number of substantial-sized studies, many showing survival effects and it seems premature to place an AIIB, supported by a small database, on an equal footing. Ongoing studies of other AIIB's may alter that conclusion.


Robert Temple, M.D.

cc:
HFD-101/R Behrman
HFD-101/R Temple
drafted:sb/7/23/02
final:sb/7/23/02
Filename:Valsartan_MM_Jul02.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple
8/14/02 02:18:51 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

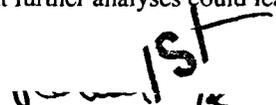
DATE: October 24, 2001

FROM: Robert J. Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: NDA 20-665/SE1-016 (capsules); 21-283/SE1-001 (tablets); Valsartan (Diovan), Novartis

TO: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

My views on the data from the Val-HeFT study of valsartan in CHF are fully described in the attached insert for an approvable letter on the referenced supplements. The approvable letter asks for an additional study of valsartan in non-users of ACEI's but leaves open the possibility that further analyses could lead to a conclusion that valsartan is effective in people who are not receiving an ACEI.


Robert J. Temple, M.D.

Attachment

cc:

Orig. NDA 20-665/S-016
21-283/S-011

HFD-110

HFD-110/E Fromm

HFD-101/R Temple

drafted:sb/10/24/01

final:sb/10/24/01

Filename:Valsartan_MM_Oct01.doc

I would like to explain in some detail the reasons we believe (1) valsartan cannot be approved as add-on therapy for patients already receiving an appropriate dose of an ACEI and (2) another study, or possibly additional analyses, is needed before valsartan can be approved for patients not receiving an ACEI. I will first summarize the available data, then consider each potential claim.

1. The Val-HeFT Study Design

Val-HeFT was a well-designed, multicenter, multinational, large (n=5010) placebo-controlled trial comparing valsartan 320 mg (if tolerated) with placebo in patients with symptomatic CHF and EF < 40%, LVID > 2.9 cm/m². This was a "real world" study and participating physicians determined the background treatment for CHF, including ACEI's (most), beta blockers (about one-third), diuretics (most), digoxin, nitrates (about one third), and spironolactone (about 5%). The doses of background therapy were not specified and were also chosen by study participants.

Val-HeFT specified two primary endpoints: (1) All cause mortality and (2) all cause mortality plus morbid events, the latter defined as resuscitated sudden death, hospitalization for CHF, or need for I.V. inotropes or vasodilators for ≥ 4 hours without hospitalization. As it turned out, almost all non-fatal morbid events were CHF hospitalizations. Because there were 2 primary endpoints and multiple interim analyses, the critical alpha for morbidity was set at 0.025 and for mortality at 0.020.

Val-HeFT had an exercise (6 minute walk) substudy in about 600 patients and several secondary endpoints: heart failure hospitalizations, NYHA classification, various signs and symptoms of CHF, including edema, rales, PND, DOE, fatigue, orthopnea, venous distension, 3rd heart sound and the Minnesota Living with Heart Failure (LHFQ) scale.

Although as a general matter, we admire "real world" studies, in the present case, this approach represents a significant problem. There are two quite distinct ways in which an AII blocker could provide clinical benefit:

- (1) AII blockade could add to the effect of a full dose of ACEI (adding to a sub-optimal dose of ACEI would be possible, of course, but would not constitute effectiveness any more than would a study showing that another ACEI added to a suboptimal dose of ACEI produced an effect). There is theoretical support for such a benefit but it cannot yet be considered strong, although it is certainly plausible.
- (2) AII blockade could substitute for ACE inhibition. The theoretical support for this effect seems quite strong.

Unfortunately, Val-HeFT entered a population that does not clearly address the first possibility, as not all patients were on any ACEI and the average ACEI doses were at or below the recommended ACEI CHF doses, raising the possibility that many were not on an adequate ACEI dose. If patients were not on an adequate dose of ACEI, any benefit seen of valsartan would not represent an added effect.

Whether Val-HeFT can address the second possibility even though that possibility was not a major aim of the study, will be addressed below.

2. Val-HeFT Results

Val-HeFT gave the following results (Novartis numbers) on primary endpoints and subgroups.

	HR/p-value		
	All Val-HeFT	On ACEI	No ACEI
Mortality	1.02/0.801	1.055/0.346	0.669/0.017
Morbidity	0.87/0.009	0.901/0.096	0.560/0.0002
Non-Fatal Morbidity	0.725/0.00001	0.755/0.00026	0.462/0.0004
CV Mortality	1.012/0.857		
CHF Hospitalization	0.725/0.00001		
NYHA Class	/0.001		
Edema	/0.003		
Rales	/ <0.001		
PND	/0.001		
DOE	/0.001		
Fatigue	/0.008		
Orthopnea	/0.109		
LHFQ	/0.005		/0.095
EF	/0.001		

As you can see, we do not have complete data on the patients divided by ACE/no ACE but a preliminary analysis of the ACE yes vs. ACE no results for signs and symptoms suggests that for almost every case the HR was more favorable for the No ACE group.

It also appears that, although the 6 minute walk substudy was negative overall, in the small number of subjects not on ACEI's, results favored valsartan. This subset will need a more detailed submission/analysis.

3. Evaluation

a. Use in addition to standard therapy

We do not believe Val-HeFT supports an overall claim for treatment of CHF in patients on or not on various treatments (ACEI's, beta blockers) with the implication that valsartan adds to the effect of those agents. There is plainly no effect on mortality and the significant ($p=0.009$) effect on morbidity is driven by the no ACE subgroup. In the ACEI-receiving group (a 4600 patient subgroup), there is a trend favoring valsartan but no significant finding. Although in most cases we are chary of such subset findings, in the present case the ACEI and no ACEI groups differ in so fundamental a way that the difference (a statistically significant interaction) cannot be ignored.

I do note that there is a favorable effect of valsartan on non-fatal morbidity in the ACEI-receiving group (although not nearly as favorable as in the no-ACEI group), but this must be considered in light of the low doses of ACEI received by many patients.

I also note that Val-HeFT was intended to be one of two studies supporting effectiveness studies 107 and the Val-HeFT exercise substudy were to provide further support.

Finally, the apparent interaction with beta blockers is disturbing. The addition of valsartan to a beta blocker in the presence of an ACEI showed an adverse, nominally significant, survival effect and an adverse trend on morbidity. This outcome is not easily explained, but, again, argues against adding valsartan to an ACEI.

b. Use as a substitute for an ACEI

Val-HeFT was plainly not planned as a study to support use of valsartan as a substitute for an ACEI, for example, in people who cannot tolerate an ACEI. Nonetheless, it is that use that is best supported by Val-HeFT. The overall significant effect of valsartan on morbidity (albeit in a single study at p about 0.01) allows some license in considering the subset findings and the findings in the no ACEI are moderately strong for the Val-HeFT endpoints [low hazard ratios for survival, non-fatal morbidity, and their sum, as well as (probably, but full analyses are not yet available) the secondary endpoints (signs and symptoms, LHFQ, EF, NYHA classification)]. It also appears that valsartan improved exercise capacity in the Val-HeFT exercise substudy, but again we need to see these data.

At this time, we believe the Val-HeFT "no ACEI" data represents a single study suggesting effectiveness in patients not receiving ACEI's and there seems to be no problem in patients on, or not on, a beta blocker as well. This single study, a subset finding from a much larger study (but, again, one that met its primary endpoint, enhancing the credibility of the subset observation) does not appear to constitute the substantial evidence of effectiveness needed for approval. The most straightforward next step would be to conduct a further study (a variety of clinical endpoints could be acceptable) in patients who do not tolerate an ACEI. It is possible, however, that examination of the Val-HeFT exercise substudy and the many secondary endpoints in the no-ACEI patients in Val-HeFT could strengthen the subset findings further.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 12, 2001

FROM: Robert Temple, M.D.
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Valsartan CHF (NDA 20-665/SE1-016)

TO: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

I wanted to make two observations on the data provided in support of valsartan for CHF, one on the Russian study (103), the other on Valheft.

1. The Russian Study

This was a one month, placebo-controlled, hemodynamic study of 3 doses of valsartan and lisinopril. The study showed an effect on PCWP compared to placebo, and a bigger effect than 5-10 mg lisinopril; no dose-response was detected. The study is not really critical, as approval turns on Valheft (study 107), but Dr. Targum expresses a concern with its ethics that needs comment. Her concerns are described on pages 46 and 54-5 of her review. On page 46, it is noted that patients were "not allowed" to receive ACEI's for 6 months prior to the study and that ACEI's were standard therapy for CHF in the U.S. by the mid 1980's and that captopril was at least somewhat available in Russia at the time of the study. On pages 54-5, it is further noted that this raises the question of "whether the study design placed patients in a situation of receiving suboptimal therapy." Dr. Targum notes that the consent form appeared to list hydralazine and minoxidil as alternatives for CHF. Dr. Targum expresses doubt about the ethics of the trial and says she "will not entertain the results of this study in decisions involving valsartan."

The ethics of conducting trials in countries where standard U.S. therapy is not available have been debated (see, e.g., recent NBAC report). Specifically, there is disagreement as to whether patients in a trial are entitled to "best local" or "best global" therapy. I have serious doubts as to whether, given the substantial controversy, FDA (or individual FDA reviewers) should try to settle that question, but in some cases our involvement will be unavoidable (note recent discussion of placebo-controlled surfactant trials in Latin America).

The present case, however, raises no ethical dilemma. Patients were not denied treatment for 6 months. The study involves only a one month placebo period, probably acceptable even in the U.S., where ACEIs are available and standard. The 6-month period is an entry criterion, not a baseline period. Patients, to enter study 103 had to be ACEI-free for 6 months as part of their pre-study treatment. If omission of ACEI is less than satisfactory treatment (which it is), it was the result of the local health care system and was not imposed by or, so far as one can tell, contributed to by, the study. I therefore see no plausible ethical objection, unless the one-month placebo were considered unacceptable, a stretch, I think, given the fact that none of the patients was being treated in the first place.

2. Valheft

Although the results of Valheft are not overwhelming, it is really an add-on study, with valsartan added to a population that consisted mainly of ACEI's users. One might consider any effect of an All antagonist impressive in those circumstances.

	V	Plbo	HR	p-
Mortality	19.7%	19.4%	1.02	0.80
CV mort	17.0%	16.8%	1.01	0.86
Morbidity (+ mort)	28.8%	32.1%	0.87	0.009
CHF Hosp	13.9%	18.5%	0.73	<0.0001
CHF Rx	0.3%	0.3%	0.87	0.79

Morbidity = death, SD/resusc, need for ≥ 4 hour of I.V. inotrope or vasodilator, Hosp'n for CHF (there were very few SD + resusc (20-30) or need for CHF Rx (7,8). I.e., 349/367 non-fatal morbid events were CHF hospitalization.

Of interest, in addition to the primary endpoints, there was significant improvement on many measures of CHF: NYHA classification, PND, resting dyspnea, DOE, fatigue, jugular distension, edema, rales, LVEF, and LV.

The U.S./non-U.S. comparison is said to show a greater effect in foreign sites but the HR is sufficiently similar (0.91 in U.S.; 0.84 non-U.S.) to leave the comparison unconvincing. Mortality was almost identical in the U.S. and non-U.S. groups and showed no hint of a benefit from valsartan.

With respect to subgroups, valsartan had a near-significant (HR 0.92; 0.82-1.02) effect on morbidity in users of ACEI's and a striking (HR 0.51, 0.35-0.73), nominally significant effect in patients not receiving an ACEI. There was also a nominally significant mortality effect in the non-ACEI subgroup (HF 0.59; 0.37-0.91) and for non-fatal morbid events, there was a 50% reduction (14 vs. 28), which is probably significant. Valsartan had little effect in BB users and, again, a nominally significant effect in non-users (HR 0.80; 0.71-0.90). A question arises. Apart from the question of add-on to ACEI therapy, are the data strong enough to support use of valsartan in people who cannot tolerate an ACEI? There are findings on both fatal and non-fatal events (an interesting internal consistency) as well as their sum.


Robert Temple, M.D.

cc:

Orig. NDA 20-665/S-016
21-283/S-011

HFD-110

HFD-110/D Throckmorton

HFD-110/S Targum

HFD-101/R Temple

drafted:sb/10/10/01

final:sb/10/11/01

Filename:Valsartan_CHF_Oct01.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandra Benton
11/14/01 02:51:37 PM
TECHNICAL

Robert Temple
11/16/01 06:00:28 PM
MEDICAL OFFICER

Memorandum

DATE : October 15, 2001
FROM : Director, Division of Cardio-Renal Drug Products, HFD-110
SUBJECT: Non-Approvable, Valsartan for heart failure, NDA 20-665/S016 and NDA 21-283/S001, Novartis Pharmaceuticals Corporation
TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

The major study (Study 107, ValHeFT) randomized 5010 patients to placebo or valsartan (titrated from 40 to 160 mg bid) in a parallel (2 arm) design. Patients all had symptomatic congestive heart failure, ejection fraction < 40% and left ventricular internal diameter in diastole >2.9 cm/m² (systolic dysfunction). Almost any (Class 1C antiarrhythmics were excluded, but sotalol was present in 2% of the randomized population) background therapy was acceptable; whatever the patient's physician was using, as long as the dose was stable for 2 weeks prior randomization. Background medications included ACE inhibitors, beta-blockers, digoxin, diuretics, nitrates, and others. Intent-to-treat analyses were prespecified as the primary analysis. Also prespecified was to do the ITT analyses using prespecified covariates (the sponsor's and our review's numbers often differ to a mild degree because our reviewers did not use covariates in their analyses). Five interim analyses were performed. There were two primary endpoints, this combined with interim analyses required the final analysis to have a significance level of 0.02532 in order to preserve an overall 0.05 conventional value for the trial.

The results were:

	Events N(%)			
	Valsartan n=2511	Placebo n= 2499	Hazard Ratio	p-Value
All Cause Mortality	495 (19.7)	484 (19.4)	1.02 (0.90, 1.15)	0.80
All Cause Mortality [§] Plus Morbid Events*	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.97)	0.009

*Morbid events were sudden death with resuscitation, hospitalizations for heart failure, or intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. A blinded events committee adjudicated all morbid events.

§ All cause mortality is redefined in this endpoint. The endpoint is the first event be it all cause mortality or morbid events.

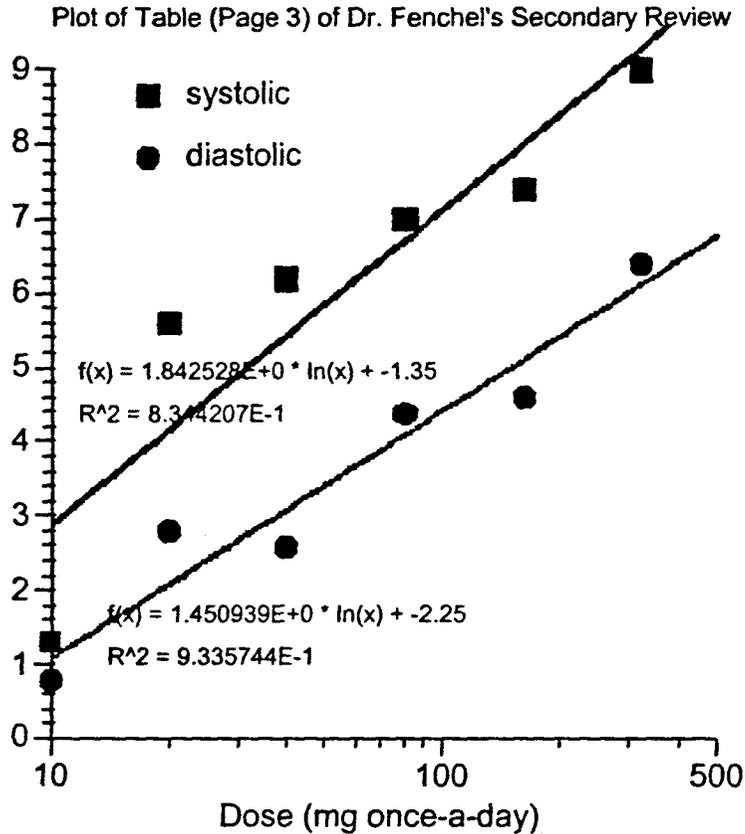
The trial clearly meets all requisite statistical and analytical criteria for having denied the null hypothesis for one of its two primary endpoints. Of course the p of 0.009 cannot be taken at face value, it is larger by some amount, but that amount is hard to precisely define. So I will refer to it as a p = 0.01, which is generous. None-the-less, there is little doubt (quantitatively, somewhere between a 5% and 1% doubt) that the trial found a treatment effect of valsartan.

Considering that 93% of randomized patients were taking ACE inhibitors and that 35 % of randomized patients were taking beta-blockers in addition to other therapies useful in the treatment of heart failure, this is a remarkable (and I would suggest, surprising) result. The results of the other four controlled clinical trials offer little direct support, so the question is - Are the results of this single trial (ValHeFT) sufficiently persuasive to warrant approval of valsartan for the treatment of patients with congestive heart failure? I think not, and that is what the rest of the body of this memorandum argues.

A Short Background on Dosing Regimens

Valsartan

When valsartan was approved (NDA 20-665) for hypertension, my transmittal memorandum contained the following figure with respect to antihypertensive dose-response. There were no side effects that were linked to increasing dose (no dose-limiting side-effects), and there is no apparent decreasing antihypertensive effect as dose is increased. As understand it, the 160 mg dosage form of valsartan is "pretty big pill" and that was a driving force with respect to upper level dosing strengths (but this is by word of mouth and has little quantitation).



This led to antihypertensive dosing recommendations that read, partially:

The recommended starting dose of Diovan is 80 mg once daily when used as monotherapy in patients who are no volume-depleted. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

Although the antihypertensive development program contained bid dosing (up to a total daily dose of 320 mg), and suggestions of a greater effect on blood pressure when administered bid, I lost the argument that dosing recommendations should include bid dosing (up to a total daily dose of 320 mg). But, a now bid (the regimen used in ValHeFT) is O.K., albeit different from the antihypertensive dosing interval recommendation.

ACE Inhibitor dosing used in ValHeFT compared to recommended dosing

<u>ACE Inhibitor</u>	<u>Mean Daily Dose In ValHeFT</u>	<u>Recommended Dose</u>
Enalapril	17.2	up to 40 mg per day
Lisinopril	18.6	up to 20 mg per day
Captopril	82.1	up to 150 mg per day

Ramirpil	5.9	up to 10 mg per day
Quinipril	21.5	up to 40 mg per day
Fosinopril	19.6	up to 80 mg per day
Benazaepril	22.1	up to 80 mg per day
Perindopril	3.7	up to 16 mg per day
Trandolapril	2.2	up to 8 mg per day
Moexipril	16.3	up to 30 per day

Ignoring the qd and bid differences that are exhibited by the above ACE inhibitors, ignoring the distribution of dosing (simply sticking with the means), ignoring the fact that we have shown all of the ACE Inhibitor maximal doses when used for the treatment of hypertension to be less than the "dose that produces maximal blood pressure lowering", it is clear that a large fraction of the patients in ValHeFT were taking doses that were between 33% and 60% of the dosing recommended in the package inserts (which I would argue are too small), except for lisinopril, which in ValHeFT was at about the package insert recommended dose.

Since none of the ACE Inhibitors have side effects that are dose limiting and that further angiotensin II blockade could be introduced with valsartan (so blood pressure on ACE inhibitors must have been O.K.), it is hard for me to understand why the doses of ACE Inhibitors were so "low". That, however, appears to be what happens in the real world in a "real world trial"/

Beta blocker dosing used in ValHeFT compared to recommended dosing

<u>Beta Blocker</u>	<u>Mean Daily Dose In ValHeFT</u>	<u>Recommended Dose</u>
Carvedilol	28.3	up to 100 mg per day
Metoprolol	64.2	up to 100 mg per day
Atenolol	42.1	up to 100 mg per day
Sotalol	149.4	up to 640 mg per day
Bisoprolol	4.6	up to 20 mg per day

Here again, I note that that the doses used were as small as 20% of those recommended.

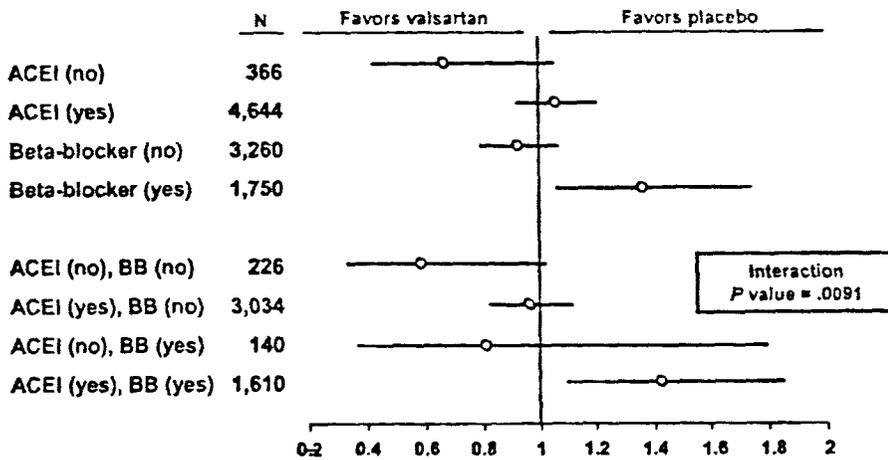
Three Subgroup Analyses (First Point)

ACE Inhibitors

Although I readily acknowledge that the best estimate of trials treatment effect comes from the ITT analysis of randomized patients, and is usually the soundest basis for decision making, I can't help but look at the results on the basis of ACE Inhibitor treatment . The best look at this comes from figures shown at the Advisory Committee by the sponsor. These are reproduced below, they are diagrams of the results of primary endpoints and were produced by the sponsor. All cause mortality was one and the other was morbidity (which was a combined endpoint of all cause mortality and "morbidity". The Interaction p value is with respect to ACE Inhibitor and beta blocker.

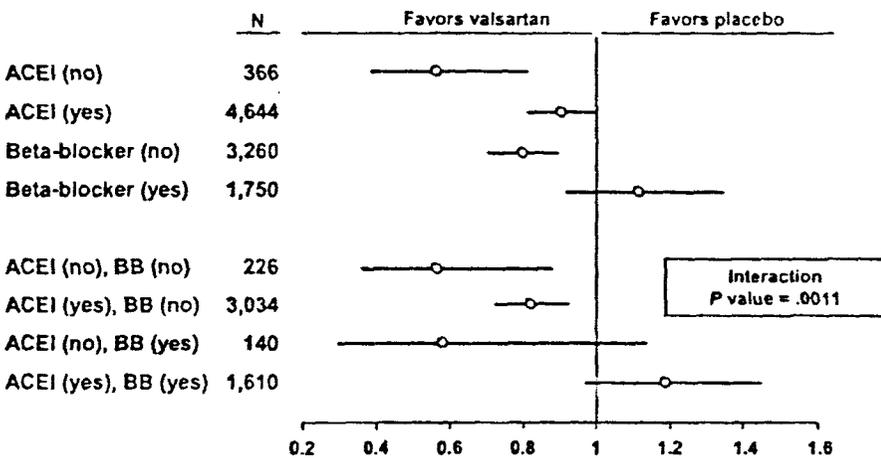
Space left blank on purpose.

Mortality by ACE Inhibitor/Beta-blocker Subgroups (Val-HeFT)



The thing that catches my eye is that the 93% of randomized patients on ACE Inhibitors has a point estimate for mortality that favors placebo. I can't escape asking the question. What if more of the patients had been on recommended doses of ACE Inhibitors? I do not think that question can be answered by the results of this trial, nor do I think the results of this trial unequivocally establish that adding valsartan to a regimen that utilizes ACE Inhibitors is "safe" from a mortality point of view — in spite of the results of one of the primary endpoints, namely all cause mortality. I am perfectly free to speculate that for those patients that are receiving maximally recommended doses of ACE Inhibitors the mortality lower confidence would be to the right of 1.0 (more of an adverse effect).

Morbidity by ACE Inhibitor/Beta-blocker Subgroups (Val-HeFT)



Gee, how does one get a p value of 0.009 from the 4,644 patients (93% of those randomized) that were receiving (less than optimal, my opinion) doses of ACE Inhibitors when the upper 95% confidence interval show little white space from 1.0 on the above graph? Although I do not assert that this subgroup analysis destroys the finding of the primary endpoint, I think it materially decreases the strength of evidence (for shorthand, it moves the p of 0.009 a lot closer to a p of 0.05 than did my previous adjustment to a p of 0.01). An additional reason to not do the usual thing, namely make decisions based on the primary endpoint.

Well, one could still reasonably argue that one should not put much faith in subgroup analyses and the results of the ITT analysis for all randomized patients (of this single trial) who were receiving any background therapy the physician desired (which only has an error rate of somewhere 1 and 5%) should be the basis of approval. I think not, I think there is reasonable question that the overall result could be found again, particularly if patients were receiving reasonable doses of ACE Inhibitors. Thus, although the trial found a treatment effect, one should not generalize beyond the population studied.

Beta Blockers

One could look at only the less than 35% (1,750) patients who were receiving beta blockers, again at relatively small doses (compared to those recommended). This gets to be a smaller population, an even weaker subgroup analysis, but the subgroup analyses almost show a nominally nominal statistically significant adverse effect on mortality and certainly have a point effect on morbidity that favors placebo. For safety purposes, we frequently interpret such findings as very important even when the finding does not have nominal statistical significance. Does that strengthen the strength of evidence that valsartan can be added to any patient with heart failure that is receiving any background therapy. Obviously not. So, I say, the strength of evidence that this single trial has, based on it's primary endpoint is moved even farther toward a p of 0.05 (or maybe beyond). None-the-less, I think ValHeFT did find a treatment effect by any standard criterion, so it may be useful but the strength of evidence offered by this single trial is insufficient to warrant approval.

In addition, I reiterate, that the ValHeFT finding should be regarded as a surprise and therefore I would require a greater strength of evidence than is present even when does not consider the subgroup analyses contribution to inference.

No Beta Blockers and no ACE Inhibitors

The results from less than 5% (226) of randomized patients look the best overall. What does that mean? Could it be that if patients are receiving better and better care with approved therapy, that valsartan could substitute for two drugs? A hypothesis that evolves from the subgroups (subgroups by other therapy) is that the more drugs added to the regimen, the worse results one can expect and that indeed the results can be adverse both with respect to mortality and morbidity (morbidity as defined by ValHeFT). Is that a basis for approval? I think not.

Furthermore, less than 5% of the patients studied allow any form of inference that valsartan could be a substitute for either patients that cannot tolerate ACE Inhibitors or beta blockers. Hardly the data I would feel comfortable citing to support such an approval (even though I that is how angiotensin II blockers are used in the practicing community).

Morbidity (Second Point)

As defined by ValHeFT, **morbidity** is the first event of all cause mortality, heart failure hospitalizations, sudden death with resuscitation, or intravenous therapy. The components of this endpoint are summarized in the following table

	Events N(%)		Hazard Ratio	p-Value
	Valsartan n=2511	Placebo n= 2499		
Morbidity Endpoint	723 (28.8)	801 (32.1)	0.87 (0.79, 0.97)	0.009
Components:				
Mortality	356 (14.2)	315 (12.6)		
Heart Failure Hospitalization	346 (13.8)	455 (18.2)		
Resuscitated Sudden Death	16 (0.6)	26 (1.0)		
Intravenous Therapy	5 (0.2)	5 (0.2)		

Note that the mortality component favors placebo and is different from the mortality primary endpoint, which was all mortality during the entire trial and that was more even (495 for the valsartan group and 484 for the placebo group). So the driving force for the **morbidity** endpoint is hospitalization for heart failure (cause specific hospitalization).

Now I ask what is that? Possibilities are many but include as principal thoughts:

- A change in the natural history of the disease
- Fewer symptoms.

Since, from the results of ValHeFT, I can glean no effect on mortality (in fact worry a little about excess mortality especially if patients are receiving ACE Inhibitors and or beta blockers), I cannot accept a decrease of hospitalizations for heart failure as reflecting a change in the natural history of the disease. I can readily accept a decrease of hospitalizations for heart failure as indicating that patients have less symptoms of heart failure.

So, this component of the primary endpoint is a symptom improvement endpoint (feeling better). That interpretation is certainly supported by the secondary endpoints that included NYHA class improvement, jugular venous distention improvement, edema improvement, rales improvement, improvement in paroxysmal nocturnal dyspnea, improvement in dyspnea on effort, improvement in fatigue (all with nominal p values in the 0.001 to 0.01 significant digit range).

This leads me to my second major point. The effect demonstrated by ValHeFT was symptomatic relief. I am unaware that we have ever set the precedent that symptom relief can be supported by a single trial that has a p value in the range of 0.05; maybe I could entertain such a possibility if the p value was in the range of 0.00125. ValHeFT is almost 10 times less significant than that.

Other Studies (Third Point)

Study 106

This was a parallel group (4 groups), placebo controlled dose ranging trial (40, 80 and 160 mg valsartan bid), 16 week, symptom relief trial that randomized 770 patients (192 to placebo and about 190 to each of the three dosage groups of valsartan. A little less than 50% of the patients were receiving low dose ACE Inhibitor, and a little less than 50% of patients were receiving high dose ACE Inhibitor background therapy during the duration of the trial. A few % of patients were not receiving any ACE Inhibitor background therapy. This appears very much like ValHeFT from and ACE Inhibitor point of view.

The results of six minute walk and of Living With Heart Failure Quality of life were the principal endpoints. There was no signal detected with respect to these two endpoints in this trial. For secondary efficacy variables, improvement in paroxysmal nocturnal dyspnea was less on valsartan than on placebo, as was dyspnea at rest, jugular venous pressure edema. So symptoms were not measurably changed, those mentioned in the preceding sentence were actually in the wrong direction in every valsartan dose group.

So, the results of Study 106 are not consistent with the striking symptom benefits seen in ValHeFT. From my perspective, this puts the findings of ValHeFT in some question, in spite the statistical significance seen in ValHeFT.

Please note that Study 106 was the trial designed to be the other trial (Study 106 and ValHeFT) that established a treatment effect (both at the p <0.05 level) of valsartan compared to placebo in the development plan. Study 106 did not provide that comfort, regardless of how one analyses that data (even disregarding primary endpoints).

Study 110

This was a parallel group (2 groups), active controlled (enalapril) study where six minute walk was the primary endpoint and many symptoms were secondary endpoints. Only 141 patients were randomized (71 to enalapril and 70 to valsartan). A reasonable fraction of patients were receiving beta blocker background therapy (greater than 60%) and the enalapril dose was 20 mg bid (the same as the average dose of enalapril present in background therapy in ValHeFT).

No treatment differences were detected in any variable of any interest. One should have expected to find some kind of effect, since ValHeFT claims a treatment effect over and above ACE Inhibition.

Summary of this point

ValHeFT results indicate that in presence of ACE Inhibition improvement in NYHA scores ($p=0.001$), improvement in paroxysmal nocturnal dyspnea ($p=0.002$), improvement in dyspnea on effort ($p=0.002$), improvement in fatigue ($p=0.010$), improvement in jugular venous distention ($p=0.001$), improvement in edema ($p=0.003$), improvement in rales ($p=0.001$) and improvement LHFQ overall score $p=0.004$). From my point of view, the results of Study 106 and Study 110 (not even a hint of benefit) make me hesitate to take the results of ValHeFT at face value, and moreover introduce reasonable doubt as to whether the results of ValHeFT could be reproduced if ValHeFT were repeated; in spite the statistical significance seen.

Last Point

Not a major point, but it is of some negative note that the number of days alive and out of the hospital (any reason for being in hospital) was 689.5 for the valsartan group and 687.7 days for the placebo group. Not very different, emphasizing that the effect on first admission for heart failure was the major finding. But, also saying that overall this has little impact on whether or not hospitalization might occur. Days in hospital were 9.8 days for the valsartan group and 11.0 for the placebo group, also not very different.

Conclusion

Although the single trial (ValHeFT) is entirely consistent with there being a treatment effect (a reduction of symptoms) of valsartan:

- I do not think it has the "strength of evidence" that allows this single trial to be the basis of approval.
- The two other trials of symptom benefit (Study 106 and Study 110) failed to support the symptom benefit apparently present in ValHeFT. Subgroup analyses suggest that background therapy could have a profound influence on the magnitude of benefit that could be expected from addition of valsartan to a regimen.
- Thus, overall risk/benefit in a general population of patients with congestive heart failure receiving approved treatment regimens at recommended doses cannot be reasonably evaluated.

The risk/benefit evaluation is not unimportant, since valsartan would represent the 7th drug (6 actually approved) added to an already complicated treatment regimen and the results of ValHeFT raise (but do not resolve) the possibility that favorable effects on mortality might be negated. It appears to me that this question has to be definitively answered, prior to approval. ValHeFT raises the question, but does not answer it.

This is basically a "single trial" problem. On its face, I would argue the finding of a statistically significant effect on one of two primary endpoints at a level of $p=0.009$ is strong but inadequate evidence to support an approval decision, in spite of very strong secondary endpoint findings. The strength of evidence is further undermined by:

- Two other trials that do not confirm the most important finding of ValHeFT, namely an added symptom benefit (or "superiority) to ACE inhibitors plus or minus beta blockers. So the results of ValHeFT should be considered a "surprise" and therefore should be expected to be highly significant.
- Internal inconsistency of subgroups, to the point where the sponsors conclude that the combination of ACE Inhibitors and beta blockers can have substantive adverse effects on mortality.
- The trial should be regarded more as a "feel good" trial than a trial that found effects on irreversible harm, since it mainly affected first hospitalizations for heart failure.
- The trial results do not allow a reasonable risk/benefit assessment.

Even if one considered the "strength of evidence" of this single trial sufficient for approval, and one "labeled" valsartan with full disclosure, I cannot see how anyone in the practicing community could appropriately determine which patients should actually receive therapy; I can not figure that out, so I conclude that others could not either. A draft non-approvable letter is also included in the attachments.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-283 NDA 20-655	Efficacy Supplement Type SE-1 (Patients with Heart Failure who are intolerant to ACE inhibitors)	Supplement Number 001 (Tablets) 016 (Capsules)
Drug: Diovan (valsartan) Tablets (40, 80, 160, and 320 mg) & Capsules (80 and 160 mg)		Applicant: Novartis Pharmaceuticals
RPM: E. Fromm		HFD-110 Phone # 594-5332
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		September 30, 2002
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM-10/15/01, 7/17/02, and 8/7/02
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (AE letter) () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	Labeling Discussion-July 26, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	X-40 mg strength
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (Pediatric Studies)
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	4/29/96
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	10/11/01
• 48-hour alert	Not Available
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Office Director-October 24, 2001 & July 23, 2002. Division Director-October 15, 2001 Medical Team Leader-10/18/01, 12/10/01, 12/21/01, 2/06/02 Statistical Team Leader-6/17/02
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9/13/01
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	10/10/01
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	9/13/01, 9/28/01 & 6/17/02
❖ Biopharmaceutical review(s) (indicate date for each review)	9/10/01
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) (indicate date for each review)	X
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	X 7/20/01
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: 10/11/01 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed Pending () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	7/30/01
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

RHPM NDA Efficacy Supplement Approval/Labeling Review
August 14, 2002

Diovan (valsartan) for CHF

NDA 20-665/SE1-016 (capsules)

NDA 21-283/SE1-001 (tablets)

Sponsor: Novartis Pharmaceuticals, Inc.

Classification: SE1 (new indication)

Review Classification: Priority (6 month review)

Indication: Treatment of Heart Failure

Date of Applications: April 27, 2001 (20-665/S-016)
July 23, 2001 (21-283/S-001)

Date of 1st AE Letter: October 24, 2001

Date of 2nd AE Letter: July 23, 2002

Date FPL Submitted: July 29, 2002

Date FPL Received: July 30, 2002

User Fee Goal Date: September 30, 2002

Background

An approvable letter was issued on October 24, 2001 for valsartan for CHF for both NDA 20-665/S-016 and NDA 21-283/S-001. After additional analyses of the Val-HeFT (Valsartan Heart Failure Trial) data for no-ACEI patients were submitted that confirmed the strong morbidity and mortality effects in this subset, an approvable letter with marked-up draft labeling was issued on July 23, 2002. The letter stated that Diovan (valsartan) Capsules and Tablets would be indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant to an ACE inhibitor. The letter also notes that NDA 21-283/S-001 provides for a new 40 mg tablet strength

Novartis submitted revised labeling on July 24, 2002 that was discussed at a teleconference with the Agency on July 26, 2002. At this telecon, the Agency agreed that the revised labeling submitted on July 24, 2002 was acceptable (with a few minor revisions) and that the sponsor could submit final printed labeling (FPL).

Review

Novartis submitted final printed labeling for both supplements on July 29, 2002. When compared with the last approved labeling supplements (S-008 for NDA 20-665 & S-002 for NDA 21-283), the following changes were noted:

1. Under **CLINICAL PHARMACOLOGY, Special Populations**, a new **Heart Failure** heading has been added that reads as follows:

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.

2. Under **CLINICAL PHARMACOLOGY, Pharmacodynamic and Clinical Effects**, this subsection has been subdivided into **Hypertension** and **Heart Failure** subheadings. The information under **Hypertension** remains unchanged from the previously approved labeling while the results from the Val-HeFT trial have been inserted under the **Heart Failure** subheading.
3. Under **INDICATIONS AND USAGE**, this section has been subdivided into **Hypertension** and **Heart Failure** subheadings. The indication for **Hypertension** remains unchanged from the previously approved labeling while a new indication has been added under **Heart Failure**. The new indication reads as follows:

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).

4. Under **WARNINGS**, the subsection that was titled **Hypotension in Volume and/or Salt-Depleted Patients** has been renamed to **Hypotension**. This information in this section remains the same as the previously approved labeling with the exception of the word "excessive" which was added to the first sentence of the second paragraph.

A new subheading has been added that it is titled **Hypotension in Heart Failure Patients** and reads as follows:

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.

5. Under **PRECAUTIONS**, new subheadings titled **Impaired Renal Function – Heart Failure** and **Concomitant Therapy in Patients with Heart Failure** have been added. Information from the Val-HeFT trial has been added beneath the **Impaired Renal Function – Heart Failure** subheading and an important warning has been added to the new **Concomitant Therapy in Patients with Heart Failure** which recommends against the concomitant use of Diovan, an ACE inhibitor, and a beta blocker together. The combination of the 3 drugs together has been associated with an unfavorable heart failure outcome.

6. Under **PRECAUTIONS, Drug Interactions**, a 4th paragraph has been added to this subsection that reads:

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

7. Under **PRECAUTIONS, Geriatric Use**, this subsection has been updated to include the Val-HeFT data for patients >65 years old and now reads as follows:

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.

8. Under **ADVERSE REACTIONS**, new subheadings of **Hypertension** and **Heart Failure** have been added. The information pertaining to the **Hypertension** subsection has not changed since the previously approved labeling but new adverse event information from the Val-HeFT trial has been added in both tabular and text form to the **Heart Failure** subsection.
9. Under **DOSAGE AND ADMINISTRATION**, new subheadings of **Hypertension** and **Heart Failure** have been added. The information pertaining to the **Hypertension** subsection has not changed since the last approved labeling but new dosing information for patients with heart failure has been added that reads as follows:

Heart Failure

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

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

NDA 21-283/S-001

The above noted changes to NDA 20-665/S-016 have also been made to NDA 21-283/S-001 with the following exceptions:

1. Under **DOSAGE AND ADMINISTRATION**, new subheadings of **Hypertension** and **Heart Failure** have been added. The dosing information under the **Hypertension** subheading was recently updated via S-002, approved April 5, 2002.

The information under **Heart Failure** is the same as noted above for NDA 20-665/S-016 with the exception that the qualifier (This dose is available only in tablet form) has been removed.

2. Under **HOW SUPPLIED**, information pertaining to the 40 mg tablet has been included as well as some changes in format for this section.

Comments/Recommendations: Dr. John Simmons asked that following changes be made to the labeling at the next printing. They are: